Synthesis of Cyclic Depsipeptides under Direct Amide Cyclization Conditions

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I would like to express my deepest gratitude to
Prof. Dr. Heinz Heimgartner
for accepting me in his research group,
for the challenging topic,
for the help and support I received from him during all these years.

TO MY WIFE

Without whom it would be same,
if the depsipeptides were 7- or 14-membered…

Foreword

This Ph.D. thesis is based on the results published or being published in international scientific journals. It is presented in four chapters corresponding to the papers in as much an unchanged form of the respective manuscripts as possible. Therefore, compounds and references are numbered independently in each chapter. An overview of the entire work is given in the following summary.

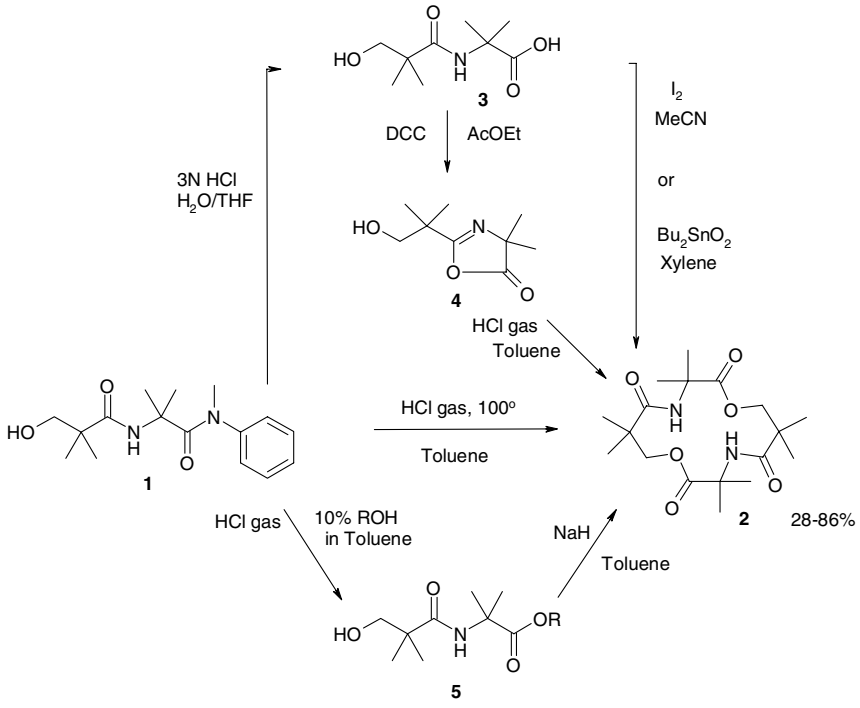
Table of Contents

SUMMARY

This work describes the use of the "direct amide cyclization" (DAC) of β-, γ-, and δ-hydroxy acid containing dipeptides, obtained by the reaction of the corresponding hydroxy acids with 3-amino-2*H*-azirines, the so-called "azirine/oxazolone" method. The goal of this work was to synthesize cyclic depsipeptides with potential biological activities and to establish the limits of the DAC.

In a short introduction the role of peptides and depsipeptides in nature is described, as well as a few of the most popular ways for their synthesis. Details about the azirine/oxazolone method and the direct amide cyclization, used throughout this work, are also given.

In chapter one, several attempts to prepare a 7-membered cyclodepsipeptide *via* DAC are described, based on analogies with syntheses of 6- and 9-membered depsipeptides. Treating amide **1,** prepared by the azirine/oxazolone method, under the DAC reaction conditions yielded, instead of the desired 7-membered ring, only its dimer **2** (Scheme 1). Variation of the concentration, temperature, reaction time and solvents led to an optimized yield of 73% for the dimeric product, whereas no monomeric product was found in any of the reaction mixtures. In order to clarify whether the twinning was a result of the chosen DAC reaction conditions, a number of classical lactonization procedures, among others the *Corey-Nikolaou* and *Mukayama* methods, were applied, but none of them led to the 7-membered depsipeptides. If a cyclic product was formed at all, it was in all cases the dimer **2**. Treatment of hydroxy acid **3** with DCC yielded oxazolone **4** in good yield, which upon subjection to DAC conditions formed **2** in excellent yield, suggesting, just as expected, that **4** is an intermediate in the DAC reaction. Thus five different methods for the synthesis of dimer **2** were elaborated, with yields varying from 26 to 86% (Scheme 1). The structures of amide **1**, cyclodepsipeptide **2**, hydroxy acid **3,** and oxazolone **4** were confirmed by X-ray crystallography.

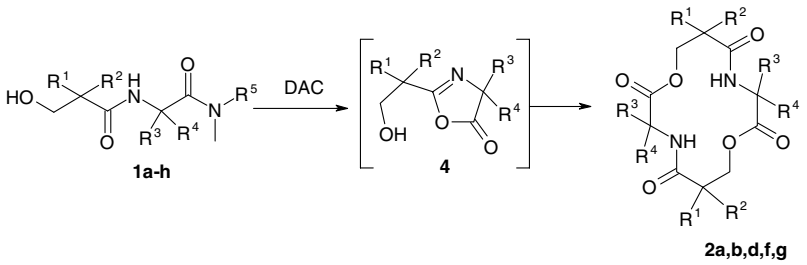


Scheme 1

In the second chapter of this work we tried to elucidate the reason for the twinning process, described in the first chapter. The substituents in the hydroxy acid as well as in the amino acid moieties were largely varied (**1a-1h**), and the attempted cyclization led in almost all cases to the 14-membered depsipeptides of type **2** (Scheme 2).

The twinning is most probably a result of the greater thermodynamic stability of the 14-membered ring compared to the 7-membered one. Another factor, which might contribute to the twinning, as suggested in the literature, is H-bond formation, which would be much weaker in a 7-membered ring.

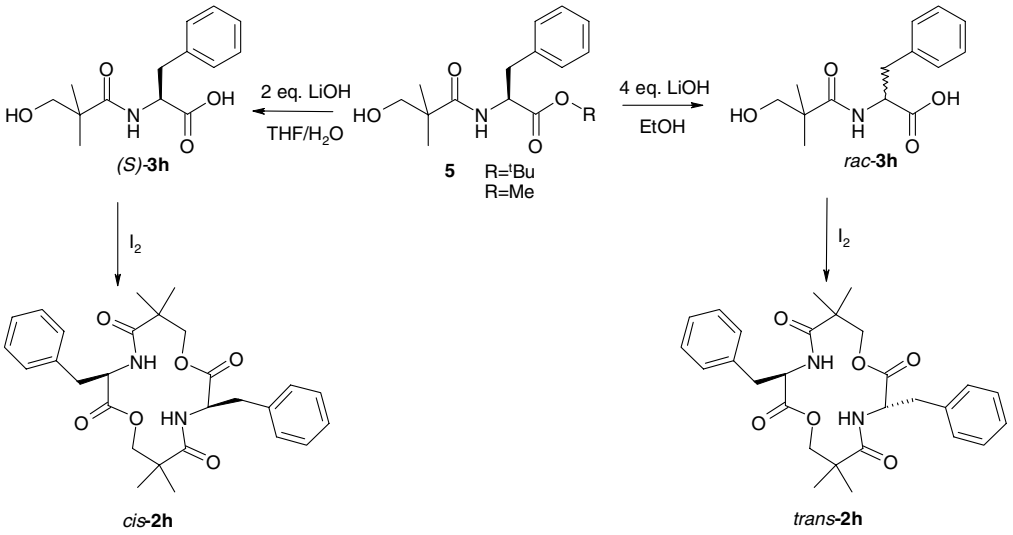
Molecular modeling using simple AM1 calculations shows that the formation of the dimeric depsipeptide is indeed favored over the formation of the monomer, but it does not explain why the 14-membered ring is the only product formed. A mixture between the monomeric and dimeric forms is to be expected.



	a	***b***	***c***	***d***	***e***	***f***	***g***	***h***
R^1	Me	Me	H	Me	H	Me	Me	Me
R^2	Me	Me	Me	Me	Ph	Ph	Me	Me
R^3	Me	Me	Me	H_2C-CH_2	Me	Me	Me	H
R^4	Me	Me	Me	H_2C-CH_2	Me	Me	Bn	Bn
R^5	Me	Ph	Ph	Me	Ph	Ph	Ph	Ph

Scheme 2

From the experiments carried out, it may be concluded that if neither of R^1-R^4 is a proton, *i.e.* both centers are disubstituted, the twinning occurs with good yields and no side products are formed. If the amino acid moiety is monosubstituted (*i.e.* R^3 = H or R^4 = H), twinning also takes place, although not *via* DAC. Treating racemic **3h** with I_2 in MeCN gives the *trans*-dibenzyl dimer, *trans*-**2h**, while (*S*)-**3h** –yields the *cis*-diastereomeric 14-membered depsipeptide *cis*-**2h** in moderate yields (Scheme 3). The structure of both cyclodepsipeptides was established by X-ray crystallography.

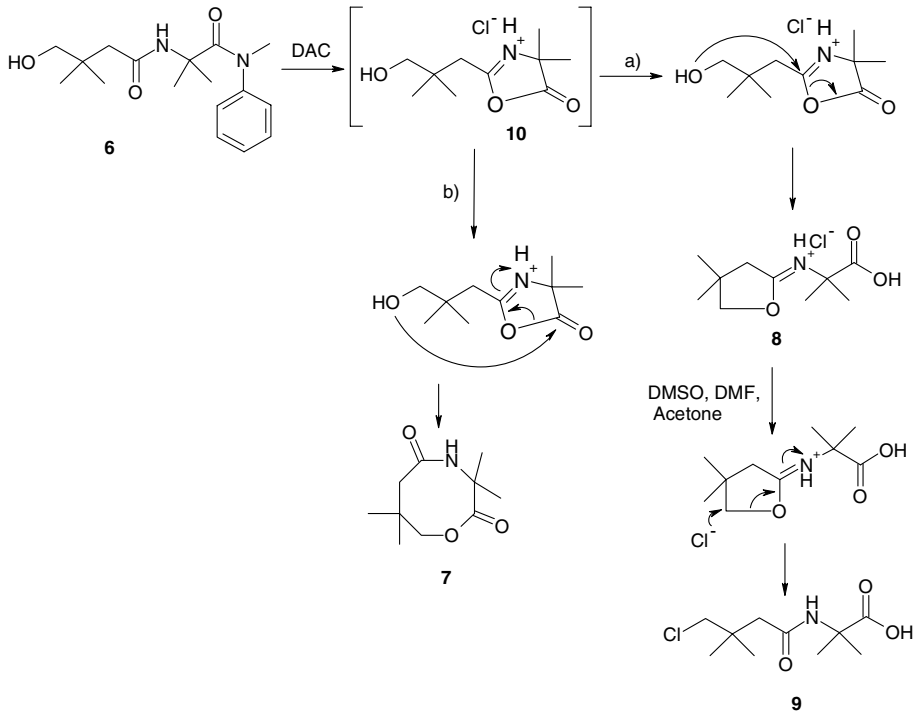


Scheme 3

If, on the other hand, the hydroxy acid moiety is monosubstituted (*i.e.* R^1 = H or R^2 = H), the formation of the intermediate oxazolone under DAC conditions could be monitored by IR spectroscopy, but then elimination of water occurs and no cyclic depsipeptides could be isolated.

The third chapter is a direct follow-up of the first two, extending the use of the DAC on depsipeptides containing γ-hydroxy acids, which could potentially yield 8-membered cyclic depsipeptides or their cyclic dimers. The starting materials for the cyclization were again synthesized by using the azirine/oxazolone method and γ-hydroxy acids. But the DAC of amide **6** did not lead to the desired products (*e.g.* **7**), but instead to the 5-membered imino lactones **8** or the chlorinated acids **9**, (Scheme 4).

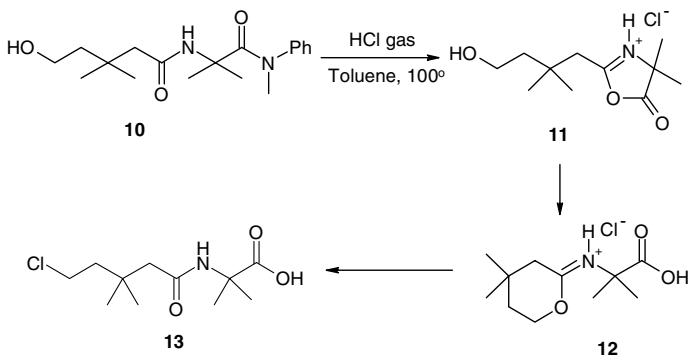
The formation of these unexpected products can be explained as follows. The initially formed oxazolone **10** possesses two electrophilic centers – the carbonyl and the imino C-atom, and the OH group can attack either one of them. Attack on the CO-group (path b) would lead to the desired 8-membered cyclodepsipeptide **7**, whereas the attack on the imino group (path a) leads to the isolated imino lactone **8**. Apparently, the formation of a 5-memberd ring is preferred to the formation of the 8-membered one.



Scheme 4

In polar solvents and/or in the presence of silica gel, the hydrochloride **8** of the imino lactone isomerizes to the chlorinated acids **9**, presumably *via* S_N2 attack of the chloride ion. Stabilization of imino lactones **8** was achieved by introducing additional substituents into the ring, which prevent ring opening to give **9**, but still no cyclic depsipeptides could be isolated. The structures of both **8** and **9** were confirmed by X-ray crystallography.

In the last chapter, the 'direct amide cyclization' conditions were applied to the linear precursor **10,** which contains a δ-hydroxy acid. The expected product in the case was either the 6-membered imino lactone **12**, analogous to **8**, or a 9-membered cyclodepsipeptide. As a 9-membered cyclodepsipeptide has already been synthesized *via* DAC from an α-hydroxy acid containing linear precursor, the formation of chloro acid **13** as the sole product was a surprise (Scheme 5).



Scheme 5

The formation of **13** proceeds most probably *via* the intermediate 1,3-oxazololone derivative **11** and the 6-membered imino lactone **12**, which obviously is unstable under those conditions and, in analogy with **8,** isomerizes spontaneously to the chloro acid **13.** Thus, the dependence of the result of the DAC reaction on whether an α-, β-, γ-, or δ-hydroxy acid diamide is used has been confirmed.

It may be concluded that the direct amide cyclization is an appropriate method for the synthesis of cyclic depsipeptides only if the terminal OH group is in α- or β-position of the hydroxy acid.

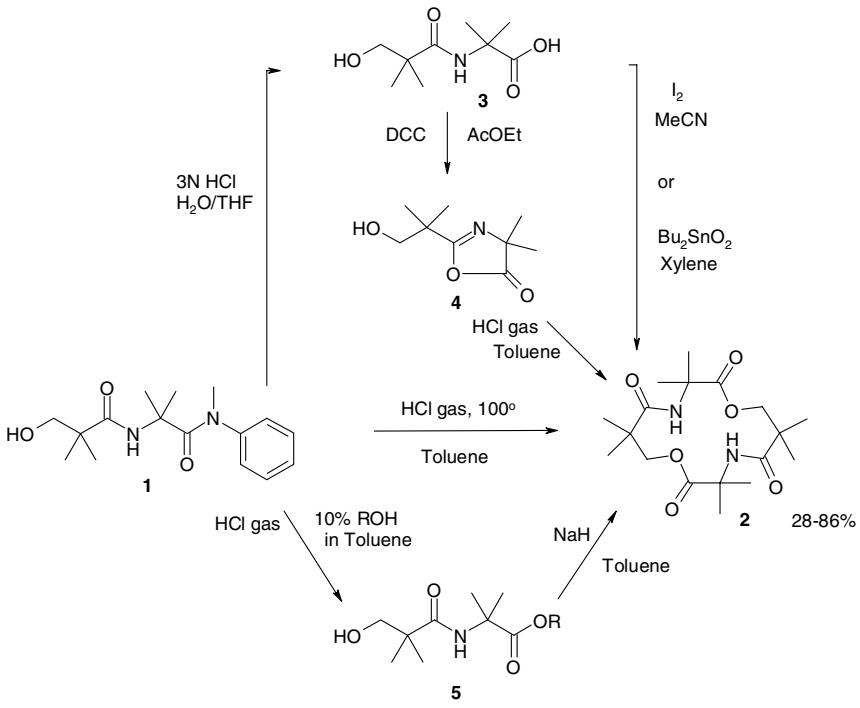
ZUSAMMENFASSUNG

Diese Arbeit beschreibt die Anwendung der "Direkten Amidzyklisierung" (DAC) von β-, γ- und δ-Hydroxysäure enthaltenden Dipeptiden zur Synthese von zyklischen Depsipeptiden. Die verwendeten Dipeptide wurden durch die Reaktion der entsprechenden Hydroxysäuren mit 3-Amino-2*H*-azirinen, der so genannten "Azirin/Oxazolon Methode", hergestellt. Das Ziel dieser Arbeit war die Synthese zyklischer Depsipeptide mit potentieller biologischer Aktivität. Im weitern wurden auch die Grenzen der Reaktion untersucht.

In einer kurzen Einleitung wird die Bedeutung der Peptide und der Depsipeptide in der Natur, sowie einige der populärsten Methoden für ihre Synthese beschrieben. Es folgt eine Übersicht über die in dieser Arbeit verwendete "Azirin/Oxazolon Methode", und die "Direkte Amidzyklisierung".

Im ersten Kapitel werden, in Anlehnung an vorherige Synthesen von 6- und 9-gliedrigen Depsipeptiden, einige Versuche beschrieben, die zu einem 7-gliedrigen Zyklodepsipeptiden führen sollten. Das durch die "Azirin/Oxazolon Methode" hergestellte Amid **1** lieferte jedoch bei der Reaktion unter DAC Bedingungen anstelle des gewünschten 7-gliedrigen Ringes ausschliesslich den 14-gliedrigen Ring **2** (Schema 1).

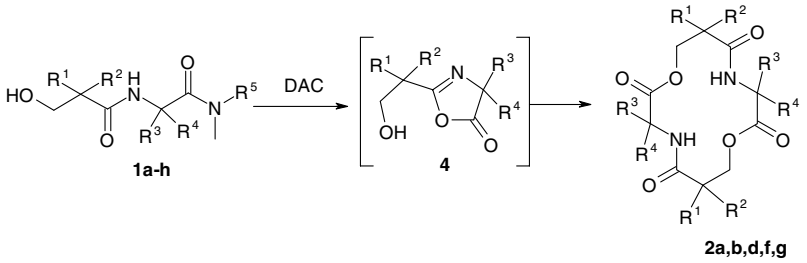
Änderungen der Konzentration, der Temperatur, der Reaktionszeit und des Lösungsmittels führten zu einer optimierten Ausbeute von 73% für das Zyklodimer. Dabei wurden keine Hinweise für die Bildung eines monomeren zyklischen Produktes gefunden. Zur Klärung der Frage, ob diese Dimerisierung ein Resultat der gewählten Reaktionsbedingunen war, wurden eine Anzahl von klassischen Lactonisierungsverfahren, unter anderem die *Corey-Nikolaou* und *Mukayama* Methoden, angewendet. Keine dieser Methoden führte aber zu den gewünschten 7-gliedrigen Depsipeptiden. Wenn überhaupt ein zyklisches Produkt gebildet wurde, war es immer das Dimer **2**.



Schema 1

Behandlung der Hydroxysäure **3** mit Dicyclohexylcarbodiimid (DCC) ergab das Oxazolon **4** in guten Ausbeuten, welches nach Reaktion unter den DAC Bedingungen das Dimer **2** in ausgezeichneter Ausbeute bildete. Dies deutet, wie erwartet, darauf hin, dass **4** ein Intermediat in der DAC Reaktion ist. Insgesamt wurden fünf unterschiedliche Methoden zur Synthese des Zyklodimers **2** entwickelt, deren Ausbeuten von 26% bis 86% reichen (Schema 1). Die Strukturen von Amid **1**, Zyklodepsipeptid **2**, Hydroxysäure **3** und Oxazolon **4** wurden mittels Röntgen Kristallographie bestätigt.

Im zweiten Kapitel dieser Arbeit versuchen wir, die Hintergründe der im ersten Kapitel beschriebenen Zyklodimerisierung ("Twinning") aufzuklären. Die Substituenten in den Hydroxysäure- sowie in den Aminosäureeinheiten wurden variiert (**1a**-**1h**), und die Zyklisierungsversuche führten in fast allen Fällen zu Bildung der 14-gliedrigen Depsipeptide vom Typ **2** (Schema 2).



	a	***b***	***c***	***d***	***e***	***f***	***g***	***h***
R^1	Me	Me	H	Me	H	Me	Me	Me
R^2	Me	Me	Me	Me	Ph	Ph	Me	Me
R^3	Me	Me	Me	H_2C-CH_2 H_2C-CH_2	Me	Me	Me	H
R^4	Me	Me	Me		Me	Me	Bn	Bn
$\mathbf{R^5}$	Me	Ph	Ph	Me	Ph	Ph	Ph	Ph

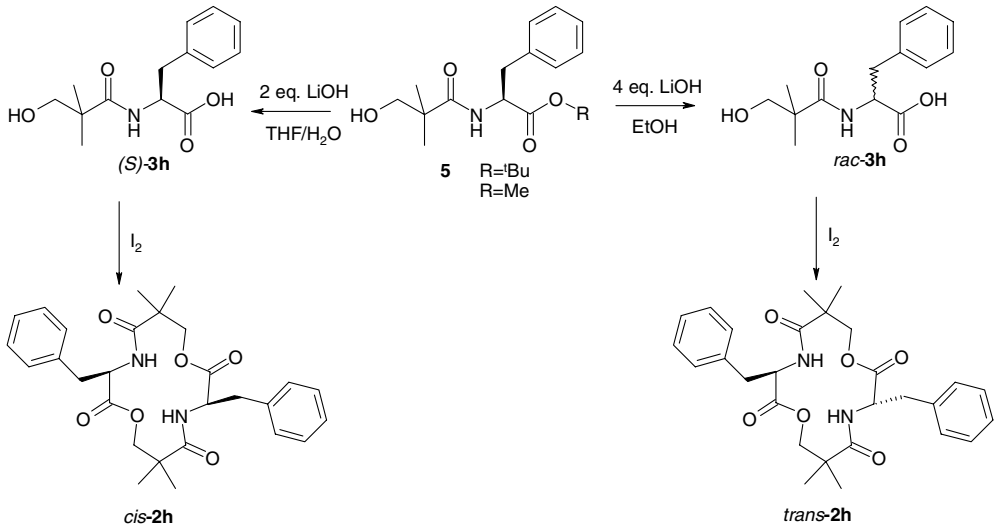
Schema 2

Das "Twinning" ist vermutlich eine Konsequenz der grösseren thermodynamischen Stabilität des 14-gliedrigen Ringes im Vergleich mit dem 7-gliedrigen. Ein weiterer Faktor, der wie in der Literatur erwähnt, ursächlich mit der Dimerisierung in Zusammenhang stehen könnte, ist die Bildung unterschiedlich-stabiler H-Brücken in 7- und 14-gliedrigen Ringen.

Mit einfachen AM1 Berechnungen konnte gezeigt werden, dass die Bildung des zyklischen Dimers in der Tat gegenüber der Bildung des zyklischen Monomers bevorzugt wird, aber sie erklären nicht, warum der 14-gliedrige Ring das einzige Produkt der Reaktion ist. Eine Mischung zwischen dem Monomeren und dem Dimeren wäre zu erwarten.

Aus den durchgeführten Experimenten kann man schliessen, dass, wenn sowohl die α-Stelle der Amino- als auch der Hydroxysäure disubstituiert ist, d.h., wenn keiner der Reste R^1 bis R^4 ein Proton ist, die Zyklodimerisierung mit guten Ausbeuten verläuft und es keine Nebenprodukte gebildet werden. Wenn dagegen die Aminosäureeinheit monosubstituiert ist (d.h. entweder R^3 = H oder R^4 = H), findet die Zyklodimerisierung immer noch statt, jedoch nicht unter den DAC Bedingungen. Das Behandeln von racemischem **3h** mit I_2 in MeCN gibt das *trans*-Dibenzyl Dimer, nämlich *trans*-**2h**, während (*S*)-**3h** unter den gleichen Bedingungen das 14-gliedrige *cis*-

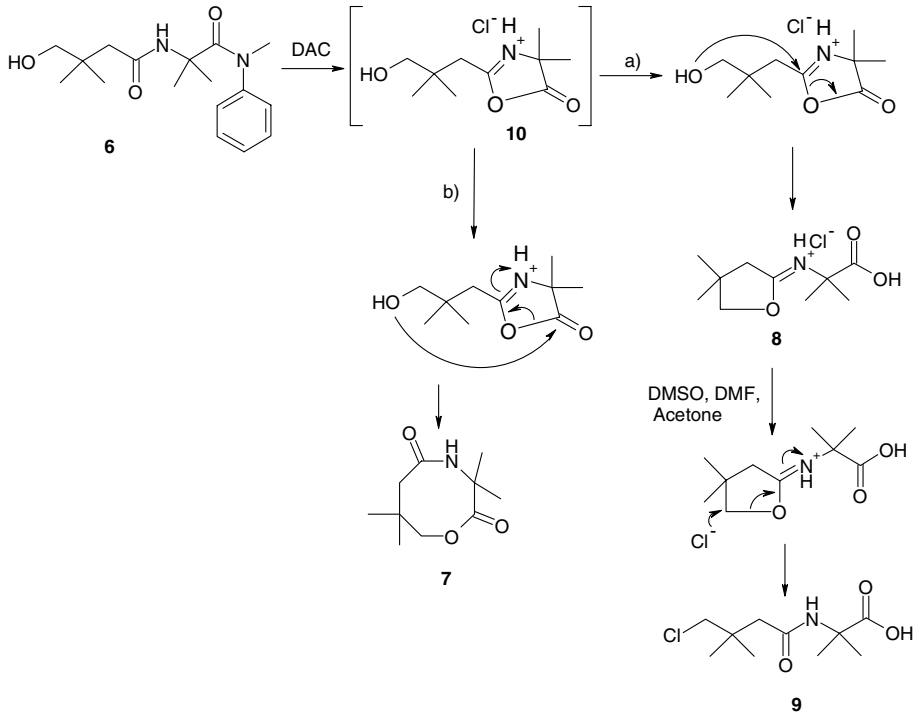
2h in mässigen Ausbeuten ergibt (Schema 3). Die Strukturen beider Cyclodepsipeptide wurden durch Röntgen Kristallographie bestätigt.



Schema 3

Wenn aber die Hydroxysäureeinheit monosubstituiert ist (d.h. entweder R^1 = H oder R^2 = H), kann zwar die Bildung des Zwischenproduktes **4** unter DAC Bedingungen mittels IR Spektroskopie verfolgt werden, leider findet dann in diesem Fall eine Wasserabspaltung statt und es kann kein zyklisches Depsipeptid isoliert werden.

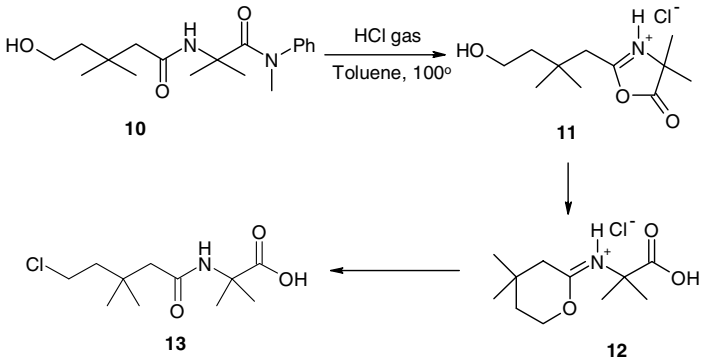
Das dritte Kapitel schliesst direkt an die ersten zwei an und untersucht die Anwendung der DAC-Methode auf γ-Hydroxysäure-enthaltende Depsipeptide, welche zu 8-gliedrigen Zyklodepsipeptiden oder ihren zyklischen Dimeren führen könnten. Die Ausgangsmaterialien für die Zyklisierung wurden wieder unter Verwendung der "Azirin/Oxazolon Methode" aus γ-Hydroxysäuren synthetisiert. Die DAC von Amiden des Types **6** führte nicht zu den gewünschten Produkten (z.B. **7**), sondern zu den 5-glidrigen Iminolaktonen **8** oder zu den chlorierten Säuren **9** (Schema 4).



Schema 4

Die Bildung dieser unerwarteten Produkte kann wie folgt erklärt werden: Das zuerst gebildete Oxazolon **10** besitzt zwei elektrophile Stellen, nämlich das Carbonyl- und das Imino C-Atom. Folglich kann die OH-Gruppe eines dieser beiden Zentren angreifen. Der Angriff auf die CO-Gruppe (Weg b, Schema 4) würde zum gewünschten 8-gliedrigen Zyklodepsipeptid **7** führen, während der Angriff auf die Imino-Gruppe (Weg a, Schema 4) zum Iminolacton **8** führt. In Übereinstimmung mit den bekannten Rinngschluss-Tendenzen wird die Bildung eines 5-gliedrigen Ringes gegenüber der jenigen des 8-gliedrigen bevorzugt. In polaren Lösungsmitteln und/oder in Anwesenheit von Kieselgel isomerisiert das Hydrochlorid des Iminolaktons **8** zur chlorierten Säure **9**, vermutlich über einen S_N2 Angriff des Chloridions. Eine Stabilisierung des Iminolaktons **8** und damit dessen Isolierung wurde erreicht, indem man zusätzliche Substituenten in den Ring einführte, welche die Ringöffnung verhindern. Es konnten aber keine zyklischen Depsipeptide isoliert werden. Die Strukturen von **8** und **9** wurden wiederum mittels Röntgen Kristallographie bestätigt.

Die Behandlung des linearen δ-Hydroxysäure-enthaltenden Dipeptids **10** mit der „Direkten Amidzyklizierung“ wurde im letzten Kapitel beschrieben. Das erwartete Produkt war in diesem Fall entweder das 6-gliedrige Iminolacton **12**, das in Analogie zu **8** entstehen könnte, oder ein 9-gliedriges Zyklodepsipeptid. Ein solches α-Hydroxysäure-enthaltende Zyklodepsipeptid wurde bereits mittels DAC hergestellt, deswegen war die Bildung der Chlorsäure **13** als einziges Produkt der Reaktion überraschend.



Schema 5

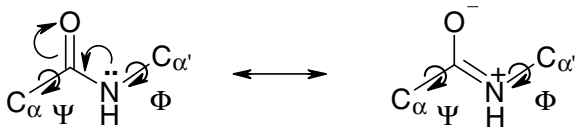
Die Bildung von **13** erfolgt sehr wahrscheinlich *via* Oxazolon **11** und Iminolakton **12,** welches unter diesen Bediengungen nicht stabil ist und zu **13** isomerisiert. Hiermit haben wir bestätigt, dass die Produkte der DAC von der Stelle der OH Gruppe in den linearen Vorläufern direkt abhängig sind. Daraus kann man schliessen, dass α- und β-Hydroxysäure-enthaltende Vorläufer die einzigen sind, die sich für die Synthese zyklischer Depsipetide via DAC eignen.

General Introduction

1. Peptides and Cyclic Peptides

1.1. Peptides

Peptides are naturally occurring oligo- and polymers of amino acids, connected by amide bonds (peptide bonds) between the carboxylic group of one building block and the amino group of the following block. This bond has an important property that has a marked effect on the rigidity of a polypeptide chain and consequently on the folding of the peptide as a whole. It has, namely, partial double bond character, which is caused by the resonance of the lone-pair electrons on the N-atom between the O- and N-atom. The consequence of this interaction is that the peptide bond is very rigid because of the higher rotation barrier along the N-CO axis. The net result is that the six atoms that are involved in the peptide bond all lie in a flat plane, *i.e*. the peptide bond freezes six atoms in a planar arrangement (*Scheme 1*).



Scheme 1

This means that the only possible free rotation in the structure is around the bonds $C_{\alpha'}$–NH (characterized by angle Φ) and C_{α}–CO (characterized by angle Ψ). This rigidity is very important with respect to the biological activity of peptides, whose biological importance cannot be overstated, for they occur in all living tissues and are fundamental to life. Enzymes, which control metabolism, γ-globulin, from which antibodies are formed and oxygen-transporting hemoglobin, are among the many peptides, on which our lives depend. Some hormones, *e.g.* insulin (controls sugar concentration in blood), oxytocin (responsible for contraction of the uterus in labour and ejection of milk from mammary glands during breast feeding) also belong to this group of biologically active substances. Further examples include opioid peptides such as endorphins and dynorphins (it is believed that they act as neutral

transmitters at nerve junctions to block pain nerve transmissions), antibiotics like bleomycin and peplomycin or toxins, like α-bungarotoxin, the main component of the cobra venom.

The formation of a peptide bond from a carboxylic group of one and the amine group of another amino acid requires, in the general case, activation of the former, as a reaction between the two does not occur at room temperature. The simplest method for the activation would be the use of acid chlorides, but their use has been limited, mainly because of "overactivation" leading to side products and epimerization. In 1955, Sheehan and Hess[1] used for the first time dicyclohexylcarbodiimide (DCC) to couple two amino acid rests together. This was the beginning of the development of the so called coupling reagents. The idea is that the acid terminus is transferred into an activated intermediate, which is not isolated, thus making it not only more susceptible to a nucleophilic attack, but also presenting a good leaving group. Some of the most commonly used coupling reagents, leading to high yields and practically no side products are shown on *Fig. 1*.

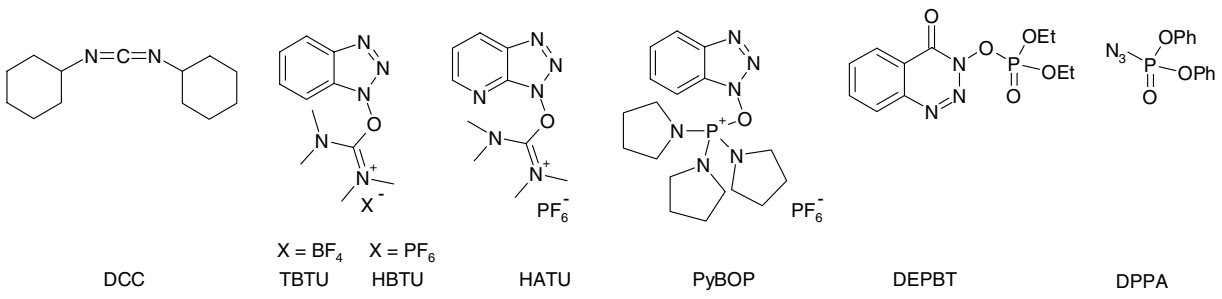
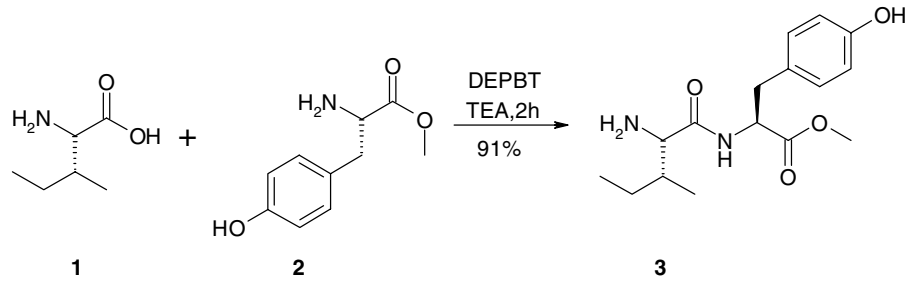


Fig.1. *Examples of coupling reagents*

Every one of these has its advantages[2], but the advantage of DEPBT is that, in contrast to some other coupling reagents, it can be used for the coupling of hydroxy acids with amino acids without the need of protecting the hydroxy group of the former[3], something which is usually recommended when using other coupling reagents. In the following example, the OH-group of tyrosine methyl ester (Tyr-OMe, **2**) may be left unprotected while coupling with isoleucine (Ile, **1**) and the dipeptide NH_2-Ile-Tyr-OMe (**3**) is formed in excellent yield, as shown in *Scheme 2*.

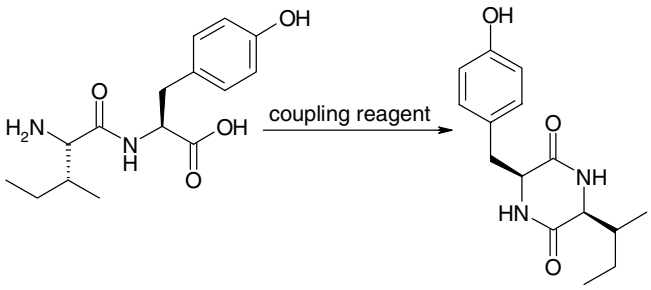


1 **2** **3**

Scheme 2

1.2. Cyclic Peptides

Cyclic peptides are formed upon formation of a peptide bond between the amino and the carboxylic termini of a linear peptide. If we take the above example, the reaction shown in *Scheme 3* would lead to the cyclic dipeptide cyclo(Ile-Tyr) **5**.



4 **5**

Scheme 3

The conversion of linear peptides to cyclic peptides has been much facilitated nowadays, because the reagents for standard amide bond formation mentioned above could also be used as cyclization promoters.

Recently reported examples involving head-to-tail cyclization (like the one between tyrosin and isoleucin) include a comparative study of the merits of various activation reagents for the synthesis of cyclosporin O[4], the DPPA-mediated cyclisation of a precursor to eurystatin A[5], various bradykinin analogues[6], the marine natural product phakellistatin 5[7], and the didemnin-like depsipeptide (-)-tamandarin A[8].

Such cyclic peptides and their derivatives continue to hold the attention of synthetic chemists and biologists alike. Apart from the occurrence in a variety of naturally occurring bioactive metabolites that possess strongly expressed and useful biological activity, cyclic peptides are often more stable *in vivo* than their linear counterparts and therefore often represent promising drug candidates. Another feature that contributes to the appeal of cyclic peptides is their reduced conformational mobility, which allows them to be used in the study and mimicry of protein folding and to present diverse functionalities in a well-defined and predictable manner.

Even the smallest cyclopeptides - the cyclodipeptides - possess biological activity. Cyclic dipeptides, also known as 2,5-dioxopiperazines, 2,5-diketopiperazines, cyclo(dipeptides), or dipeptide anhydrides, are relatively simple compounds and therefore are among the most common peptide derivatives found in nature. Curtius and Gloebel synthesized the first cyclic dipeptide, cyclo(Gly-Gly), in 1888[9]; however, their existence as a special group of compounds in nature was not recognized until early in the 20th century[10]. Between the late 1800s and early 1900s, many simple diketopiperazines were synthesized for the sole purpose of examining their interesting physicochemical properties.

Most cyclic dipeptides found to date appear to have emerged as by-products of fermentation and food processing and many are endogenous to members of animal and plant kingdoms and exhibit interesting physiological and/or pharmacological activities in mammals, but only one of these, cyclo(His-Pro), has been conclusively shown to be endogenous to mammals, and more specifically to the mammalian brain[11].

2. Depsipeptides and Cyclic Depsipeptides

2.1. Depsipeptides

Depsipeptides or depsides, *i.e.*, heterodetic peptides which contain not only an amide bond but also other types of bonds (usually an ester, *i.e.* depside bond or a disulphide bridge) as part of their backbone, are another group of peptide derivatives with interesting biological properties. Although their occurrence and pharmacological value is incomparable with that of peptides, they still represent an interesting target for drug research and development. To this class of compounds belong the obtusatic acid derivatives**,** isolated from lichens, that have antiastmatic properties,[12] as well as salicylihalamides, possessing a wide range of properties, which could be

useful to the pharmaceutical industry.[13] These include anti-cancer (*e.g.* apicularen A[14]), anabolic and antibacterial properties (*e.g.* zearalenone[15]).

2.2. Cyclic Depsipeptides

The cyclic analogues of depsipeptides have been found in many natural products and show a wide spectrum of biological activity.[16] They are therefore sought after as promising lead compounds for drug design and discovery. Nature is a rich source of the most fascinating cyclodepsipeptides, and although the significance of incorporating a depside bond is not clear, it appears to be essential for biological activity, since all-amide analogues are often inactive.[17] The depside bond is recognized as being more difficult to be incorporated into the backbone than the amide bond, so it is usually pre-formed in the linear precursor prior to cyclization at an amide bond to form the cyclic depsipeptides.

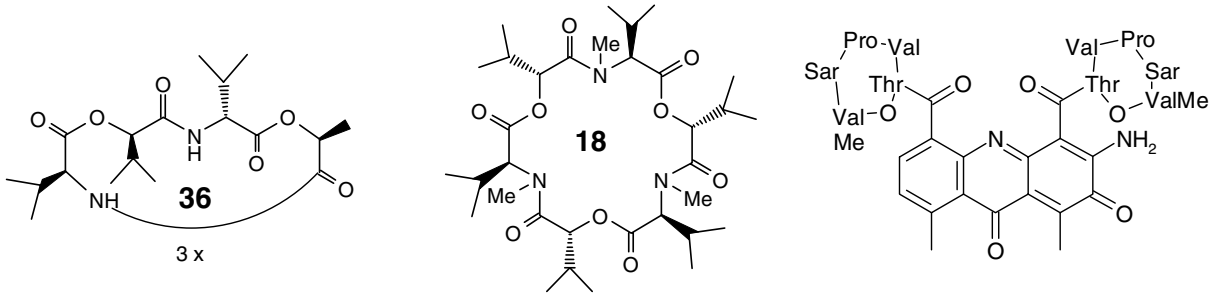
2.2.1. Biologically active Cyclic Depsipeptides

The best known structures in this category belong to the ion-selective antibiotics, valinomycin[18], the closely related enniatin family[19] and the actinomycins[20]. The common feature among them is that they all bind metal ions (as a rule of the alkali or alkaline earth group) in solution or on membrane surfaces. The resultant lipophilic complexes can freely penetrate the lipid layers of biomembranes, effecting thereby passive cation transport (along the electrical field gradient or the cation concentration gradient) across the membrane.

Probably the most important of the antibiotic-ionophores is valinomycin (*Fig. 2*). At rather low concentrations ($<10^{-8}$M) it selectively induces the potassium permeability of a wide variety of biological membranes[21]. The ionophoric properties of valinomycin are apparently responsible for its bacteriostatic action. Valinomycin is known to form more or less stable equimolar complexes with K^+, Rb^+, and Cs^+ in neutral solvents, the stability of such complexes decreasing with increase in solvent polarity. The K^+ complex is 10^4-10^3 times more stable than the corresponding Na^+ complex, the K/Na complexing selectivity of valinomycin being the highest among the known alkali metal complexones.

Valinomycin with its 36-membered ring possesses a wealth of possible conformations and elucidation of its three-dimensional structure has required considerable effort. It was the first peptide molecule of biological importance whose spatial structure was established without recourse to X-ray analysis. 3D structure elucidation was also helpful in shedding light on the

structure-function relation of valinomycin, which in turn has led to the synthesis of certain of its membrane-affecting analogs with unique properties.



Valinomycin Enniatin B Actinomycin D

Fig. 2. *Structures of Valinomycin, Enniatin B and Actinomycin D*

Enniatins (*Fig. 2*) form complexes in organic solvents not only with alkali metals, but also with alkaline earth metals and some d-metals, (*e.g.* Ag^{+}, Mn^{2+}, Zn^{2+}, Cd^{2+})[22]. Beside the typical 1:1 complexes for valinomycin, they also form 2:1 (possibly 2:3) complexes, with a notable K over Na selectivity. Such 2:1 macrocycle/cation complexes are believed to form "sandwiches", in which the most probable ligands are the amide carbonyl groups. In 3:2 complexes not only the amide carbonyls, but also the ester carbonyls interact with the complexing cation. It is believed that although enniatin complexes are less stable than those of valinomycin, this formation of non-equimolar complexes protects the cation better from the medium and anion, and makes a major contribution to the cation permeability of artificial membranes[23].

Actinomycins, the third best studies class of cyclic depsipeptides are a group of rather toxic chromopeptides manifesting both antimicrobial and antitumor properties. All of them contain the same phenoxazone chromophore group (3-amino-4,5-dicarboxy-1,8-dimethyl-2-phenoxazone) and various cyclopeptidic moieties, some of which may have very similar structures.

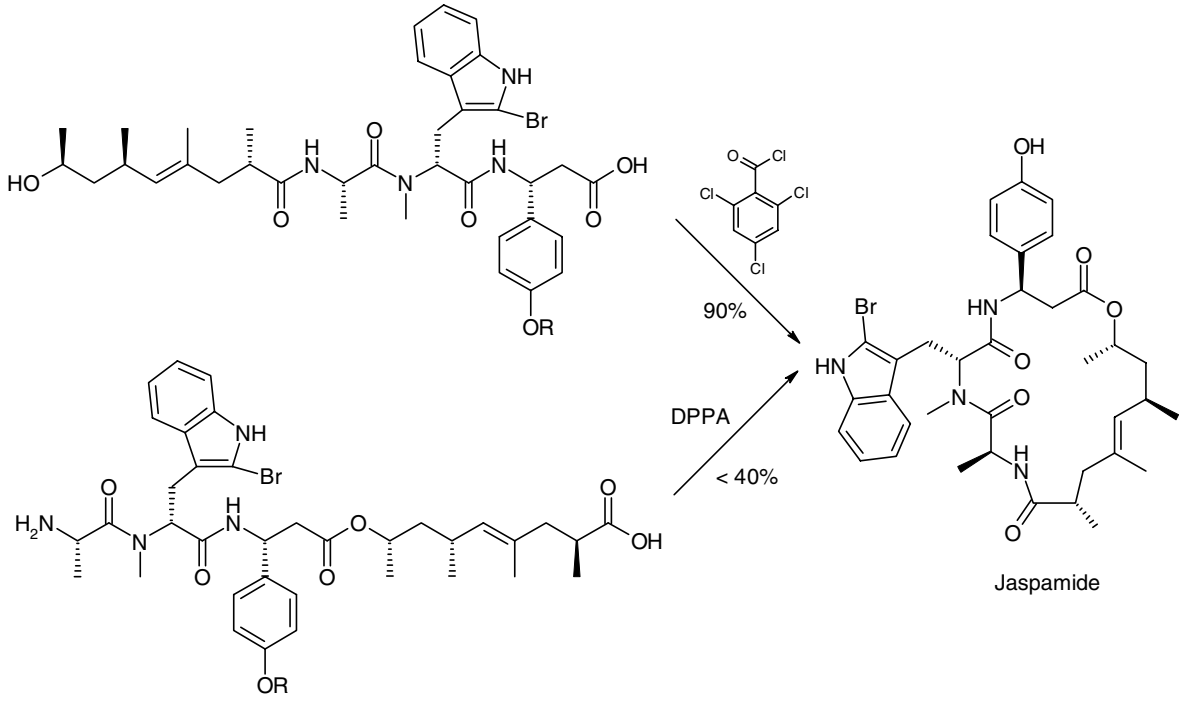
Actinomycins with two identical cyclopeptide groups are referred to as the *iso*-series, and those with differing groups—as the *aniso*-series. Actinomycin *C* (*Fig. 2*) (frequently referred to as actinomycin D) is the most readily available member of this group. It belongs to the *iso*-series and has two pentapeptide chains, containing threonine-valine-proline-*N*-Me-glycine-*N*-Me-valine. The mode of action of actinomycins involves formation of highly stable complexes with DNA, which precludes the latter from performing its biological function.[24,25]

Another interesting example represent antamanide, cyclo(Val-Pro-Pro-Ala-Phe-Phe-Pro-Pro-Phe-Phe) and several of its synthetic analogs, which also belong to the group of ionophoric antibiotics and as such are capable of complexing alkali and alkaline earth metal ions, the most stable complexes being with Na^+ and Ca^{2+}. The sodium complexing ability of the decapeptide determines its potential value as a tool for selectively inducing Na^+ permeability in biomembranes. However, in comparison with valinomycin and the enniatins it displays lower lipophilic properties and penetrates with difficulty phospholipid monolayers. This may account for the very poor ionophoric activity of antamanide. A comparison of the complexing and antitoxic properties of antamanide and its analogs has led to the conclusion that the ability to complex Na^+ (or Ca^{2+}) ions is a necessary, but insufficient condition for the manifestation of biological activity in this series of compounds[26].

Unlike all of the examples mentioned so far, phallotoxins possess a heptapeptidic ring, bridged by the side chains of the tryptophan and cysteine residues (*i.e.* they contain sulphide bridges). Their close relatives, amatoxins have a larger ring (eight amino acid residues) with two additional oxygen functions in the bridge. Both of these toxin groups are found in the poisonous *Amantia* mushrooms and they primarily affect the liver cells. Phalloidin, the best known representative of the phallotoxins, localizes in this organ immediately after administration and displays prolonged resistance to enzymatic degradation, leading to problems with its neutralization in the body. Despite the quite similar structures, phallotoxins and amatoxins have different modes of action, a good illustration of the caution required in inferences by analogy. Phalloidin impairs the membranes of the liver cells, apparently binding to the (as yet hypothetic) actin-like protein constituent, and thereby causing their aggregation into (experimentally found) filamentous structures, so that potassium ions and enzymes are released from the cell[27]. The amatoxins, whose best studied representatives are the amanitins, have a much more specific action, becoming strongly bound to one of the DNA-dependent RNA-polymerases in the eukaryotes and thus suppressing its activity. For this reason the amanitins are being widely used as a powerful tool in biochemical research[28].

2.2.2. Synthesis of Cyclic Depsipeptides

Cyclic depsipeptides are particularly well represented in the form of marine natural products. Because of their marine origins, many cyclic depsipeptides bear unusual amino acid side chains which add to their interest and synthetic complexity. Methods for the synthesis of cyclic depsipeptides vary, but for the present purpose of describing the synthesis of cyclic peptides, they can be classified into either one of two categories: those where the critical cyclization step involves formation of an ester bond (macrolactonisation) and those where ring closure involves formation of an amide bond (macrolactamisation). Until recently, the preferred cyclization step was the latter, mainly because of the multiple coupling reagents, available for peptide bond formation and widely used in normal peptide synthesis. However, there have been cases (*e.g.* Jaspamide, possessing cytotoxic, antifungal and insecticidal properties), where ester bond formation gave better results[29] (*Scheme 4*).



Scheme 4

In recent reports, where macrolactamisation is the key step *en route* to the cyclic depsipeptide, the ionophoric fungal metabolite valinomycin[30] and the marine natural product (-)-tamandarin A[9] have been prepared. In these examples, cyclization was performed in solution using HATU as the activation reagent. As examples of macrolactonisation ring closures, the work of Ranganathan[31]

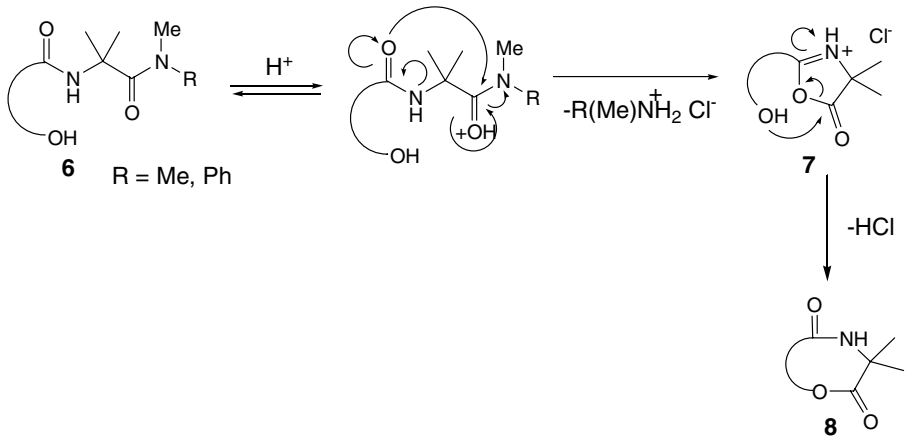
provides an interesting example of both appropriate methodology and the use of organic frameworks as conformational constraints. In these cases, linear precursors are generally reacted with appropriate dicarbonyl dichlorides to produce cyclic depsipeptides in reasonable yields. In these extensive studies,[32,33] cyclic depsipeptides containing a variety of metal-coordination sites have now been prepared. Also of interest is the production of a peptide catenane (albeit in 5% yield) using this methodology[34].

The reduction in conformational freedom brought about by cyclization often results in higher receptor binding affinity. Frequently in these cyclic compounds, extra conformational restrictions are also built in, such as D-amino acids, *N*-alkylated-amino acids or α,α-disubstituted amino acids. One of the methods for the insertion of such residues in cyclic depsipeptides is the direct amide cyclization.

3. Direct Amide Cyclization

A useful method for the ring closure of depsipeptides which contain α,α-disubstituted α-amino acids is the so-called 'direct amide cyclization' method (DAC), developed in our laboratory (Ref. *35* and references cited therein). The basic concept is that an amide of type **6** in a toluene solution or suspension is treated with dry HCl gas. Cyclization by elimination of the corresponding ammonium chloride leads to the intermediate 1,3-oxazol-5(4*H*)-one of type **7**. In the absence of other nucleophiles, the oxazolone undergoes a ring enlargement *via* intramolecular nucleophilic attack of the hydroxy group at the carbonyl C-atom of the neighboring lactone group, leading to the depsipeptide **8** (*Scheme 5).*

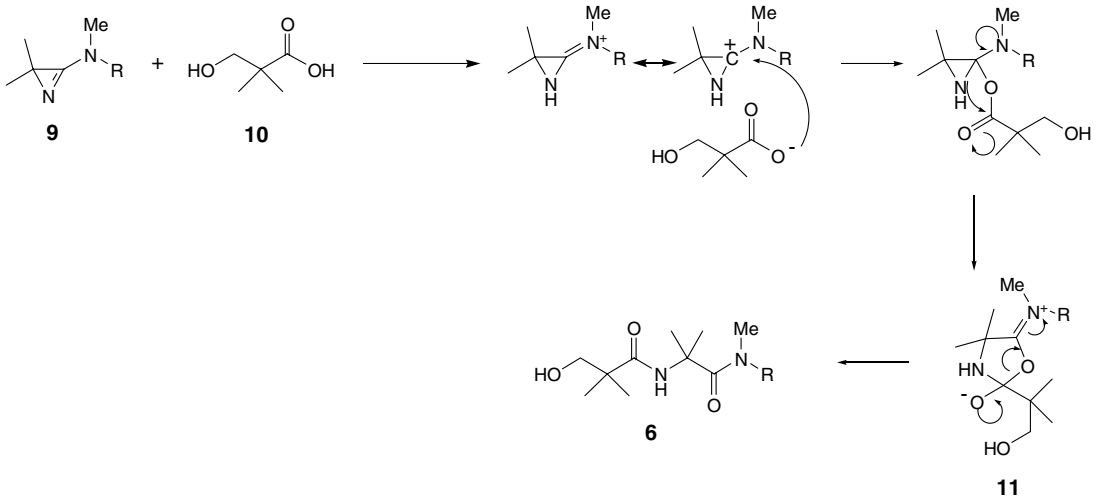
This method has been used efficiently for the synthesis of morpholine-2,5-diones (*i.e*. 6-membered cyclic depsipeptides) as well as for some 9-, 12-, 15-[36], 16-[37] and 19-[38] membered rings. For the preparation of the 6-, 9-, 12- and 15- membered rings of type **8**, the linear precursors **6** have been prepared by coupling α-hydroxy acids with 2*H*-azirin-3-amines, whereas β-hydroxy acids and 2*H*-azirin-3-amines led to the precursors of the 16- and 19-membered cyclodepsipeptides .



Scheme 5

4. Azirine/Oxazolone Method

A very useful method for incorporating α,α-disubstituted α-amino acid residues into peptides is the so called azirine/oxazolone method. The problem with the incorporation of these residues by normal coupling methods is their steric hindrance around the NH_2 group, caused by the α,α-disubstitution. Although coupling with normal coupling reagents has been proved successful, the yields are usually low and the work up is tedious. All these troubles could be avoided by the use of the azirine/oxazolone method, in which 3-amino-2*H*-azirines are used as synthons for the corresponding amino acids. When an acidic compound with a pK_a below 8 is mixed with such an azirine (**9**), the first step is the protonation of the latter. In the case of carboxylic acids (**10**), the carboxylate anion attacks in the following step the amidinium C-atom, thus activating the carboxylic group, which can be attacked by the aziridine N-atom. Opening of the three membered ring yields the zwitterionic oxazolidine intermediate **11**. Reconstitution of the carbonyl group leads to the opening of the oxazolidine, yielding the desired dipeptide (**6**). In contrast to other methods, no side products or coupling reagents have to be separated from the target molecule (*Scheme 6).*



Scheme 6

This method has been used for the incorporation of isobutyric acid, isovaline, methylvaline, methylleucine and methylphenylalanine into peptide chains (*cf.* Refs. 39 and 40 and refrences cited therein) using the following 3-amino-2*H*-azirines (*Fig. 3)*:

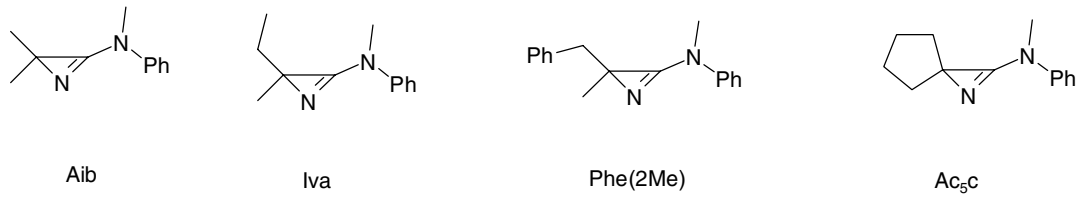
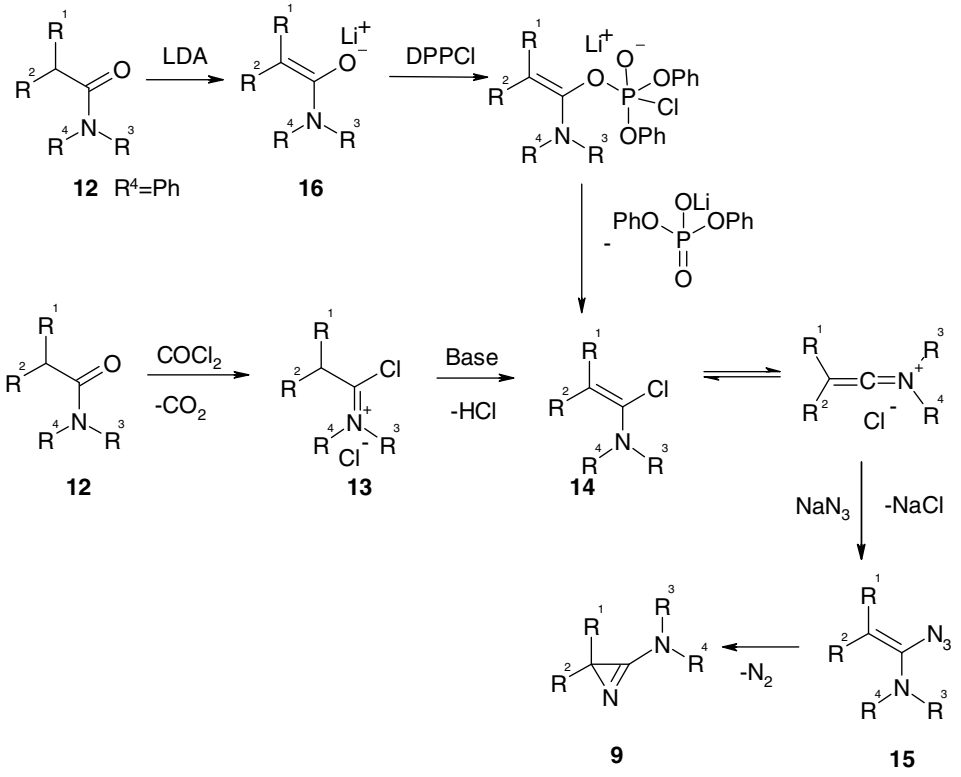


Fig. 3. *3-Amino-2*H*-azirines as synthons for α,α-disubstituted α-amino acids*

The synthesis of the corresponding 3-amino-2*H*-azirines could be achieved in a few steps, starting from the corresponding amides (*Scheme 7*). The first of the two major synthetic methods was developed in the 1970s by Rens and Ghosez[41]. It starts with N,N-disubstituted amides (**12**), with at least one α-H atom, which are treated with phosgene to yield the corresponding chloriminium chlorides **13**, which upon treatment with base loose HCl and are converted into the chloroenamines **14**. These are treated with NaN_3, leading to α-azidoenamines **15** (formed via the keteniminium salt), which eliminate nitrogen and give the desired 3-amino-2*H*-azirines (**9**) in good yields. If the amides are not reactive enough, the thioamides could be used instead, because

of higher nucleophility of the thioamide group. Another method is to treat the amide enolate **16** subsequently with diphenyl phosphorochloridate (DPPCl) to form the α-chloroenamine **14** and NaN_3, yielding the α-azidoenamines (**15**) and finally the azirine[42]. This method has proven to be efficient only with N-phenyl amides.



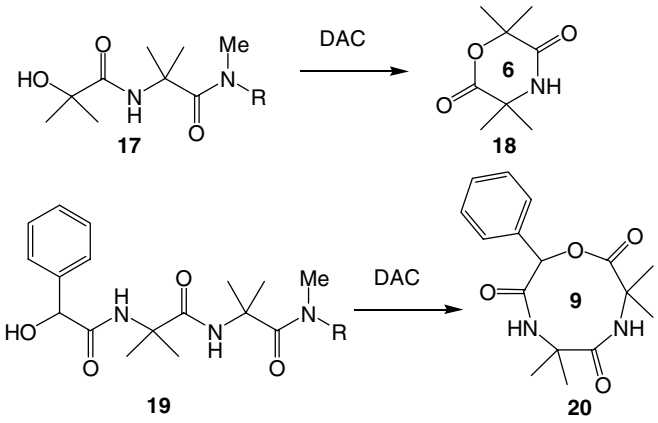
Scheme 7

5. Aim of this work

Earlier experience showed that when α-hydroxy acids are reacted with azirines, and the formed α,α-disubstituted α-hydroxy acid amides **17** are subjected to the DAC conditions, the products formed are 6-membered depsipeptides **18**[36,43]. Prolongation of the peptide chain with one more aminoisobutyric acid (Aib) unit leads to tripeptides **19**, the cyclization of which gives the 9-membered depsipeptide **20** (*Scheme 8*).

Therefore, we were interested in reacting β- and γ-hydroxy acids with azirines and cyclizing the obtained α,α-disubstituted β-hydroxy and α,α-disubstituted γ-hydroxy acid amides. Such a

cyclization should hopefully yield 7-membered depsipeptides (in the case of the β-hydroxy acid amide) and 8-membered depsipeptides (in the case of the β-hydroxy acid amide) with potential biological activity.



Scheme 8

REFERENCES

[1] J. C. Sheeham, G. P. Hess, *J. Am. Chem. Soc.* **1955**, *77*, 1067.

[2] S. Han, Y. Kim, *Tetrahedron* **2004,** *60*, 2447.

[3] P. Liu, B. Sun, X. Chen, G. Tian, Y. Ye, *Synth. Commun.* **2002**, *32*, 473.

[4] P. Li, J. C. Xu, *J. Org. Chem.* **2000**, *65*, 2951.

[5] H. Wasserman , A. K. Petersen, *J. Org. Chem.* **1997**, *62*, 8972.

[6] M. Gobbo, L. Biondi, F. Cavaggion, F. Filira, T. Piek, P. Mantel, R. Rocchi, *J.Pept. Res.* **1997**, *50*, 336.

[7] G. R. Pettit, B. E. Toki, J.-P. Xu, D. C. Brune, *J. Nat. Prod*. **2000**, *63*, 22.

[8] B. Liang, P. Portonovo, M. D. Vera, D. Xiao, M. M. Joullie, *Org. Lett.* **1999**, *1*, 1319.

[9] T. Curtius, F. Goebel, *J. Prakt. Chem.* **1888,** *37* 150.

[10] E. Abderhalden, R. Haas, Z. *Physiol*. *Chem.* **1926**, *151*, 114.

[11] C. Prasad, *Peptides* **1995**, *16*, 151.

[12] Sunil Kumar KC, K. Mueller, *Eur. J. Med. Chem*. **2000**, *35*, 405.

[13] L. Yet, *Chem. Rev.* **2003,** *103*, 4283.

[14] R. Jansen, B. Kunze, H. Reichenbach, G. Hoefle, *Eur. J. Org. Chem.* **2000**, 913.

[15] C. Cordier, M. Gruselle, G. Jaouen, D. Hughes, M. McGlinchey, *J. Magn. Res. Chem.* **1990**, *64*, 153.

[16] C. E. Ballard, H. Yu, B. Wang, *Curr. Med. Chem.* **2002**, *9*, 471.

[17] J. S. Davies, *J. Peptide Sci*. **2003**, *9*, 471.

[18] W. L. Duax, J.F. Griffin, D.A. Langs, G.D. Smith, *Biopolymers* **1996**, *40*, 141.

[19] P. Vongvila, M. Isaka, P. Kittakoop, P. Srikitikulchai, P. Kongsaeree, S. Prabpai, Y. Thebtaranonth, *Helv. Chim. Acta* **2004,** *87*, 2066.

[20] A. B. Mauger, *Top. Antibiol. Chem.* **1980**, *5*, 223.

[21] Y. Ovchinnikov, V. Ivanov, *Tetrahedron* **1974**, *39***,** 1871.

[22] V. Ivanov, A. Evstrator, L. Sumskaya, Y.Ovchinnikov, *FEBS Lett.* **1973**, *36*, 65.

[23] Y. Ovchinnikov, *FEBS Lett.* **1974**, *44*, 1.

[24] U. Hollstein, *Chem. Rev.* **1974**, *74*, 625.

[25] H. Yoo, R. Rill, *J. Mol. Recognit.* **2001**, *14*, 145.

[26] Y. Ovchinnikov, V. Ivanov, *Membrane Active Complexones, Elsevier, Amsterdam,* 1974.

[27] M. Frimmer, *Toxicol. Lett.* **1987**, *35*, 169.

[28] T. Wieland, M. Nassal, W. Kramer, G. Fricker, U. Bickel, G. Kurz, *Proc. Nat. Acad. Sci. USA* **1984**, *81*, 5232.

[29] Y. Hirai, K. Yokota, T. Momose, *Heterocycles* **1994**, *39***,** 603.

[30] O. Kuisle, E. Quinoa, R. Riguera, *J. Org. Chem.* **1999**, *64*, 8063.

[31] D. Ranganathan, *Acc. Chem. Res*. **2001**, *34*, 919.

[32] D. Ranganathan, V. Haridas, K. P. Madhusudanan, R. Roy, R. Nagaraj, G. B. John, *J. Am. Chem. Soc.* **1997**, *117*, 11578.

[33] D. Ranganathan, V. Haridas, S. Kurur, R. Nagaraj, E. Bikshapathy,A. C. Kunwar, A. V. S. Sarma, M. Vairamani, *J. Org. Chem.* **2000**, *65*, 365.

[34] D. Ranganathan, A. Thomas, V. Haridas, S. Kurur, K. P. Madhusudanan, R. Roy, A. C. Kunwar, A. V. S. Sarma, M. Vairamani, K. D. Sarma, *J. Org. Chem.* **1999**, *64*, 3620.

[35] B. Iliev, A. Linden, H. Heimgartner, *Helv. Chim. Acta* **2003**, *86*, 3215.

[36] D. Obrecht, H. Heimgartner, *Helv. Chim. Acta* **1987,** *70*, 329.

[37] K. N. Koch, A. Linden, H. Heimgartner, *Tetrahedron* **2001,** *57*, 2311.

[38] K. N. Koch, H. Heimgartner, *Helv. Chim. Acta* **2000**, *83*, 1881.

[39] T. Jeremic, A. Linden, H.Heimgartner, *Helv. Chim. Acta* **2004**, *87*, 3056.

[40] T. Luykx, A. Linden, H. Heimgartner, *Helv. Chim. Acta* **2003**, *86*, 4093.

[41] M. Rens, L. Ghosez, *Tetrahedron Lett*. **1970**, *43*, 3765.

[42] J. Villalgordo, H. Heimgartner, *Helv. Chim. Acta* **1993**, *76*, 2830.

[43] A. Linden, F. Ghorbani-Salman Pour, H. Heimgartner, *Acta Cryst. C* **2001**,*C57*, 634.

Chapter 1

An Unexpected Formation of a 14-Membered Cyclodepsipeptide[1)]

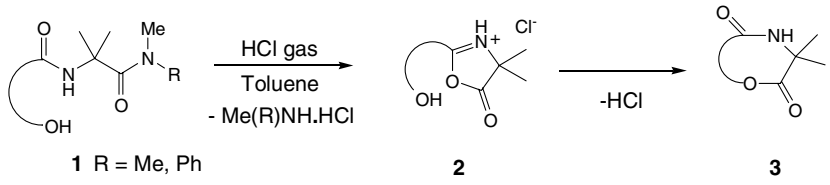
The treatment of diluted solutions of the hydroxydiamides **6a** and **6b** in toluene with HCl gas at 100^{o} gave the dimeric, 14-membered cyclodepsipeptide **10** in up to 72% yield (*Scheme 3*). The same product was formed from the linear dimer of **6b**, the depsipeptide **11**, under the same conditions (*Scheme 4*). All attempts to prepare the cyclic 7-membered monomer **9**, starting with different precursors and using different lactonization methods failed, and **10** was the only product which was formed (*Scheme 6*). For example, the reaction of the ester **20** with NaH in toluene at 80^{o} led exclusively to the cyclodimer **10**. On the other hand, the base catalyzed cyclization of the hydroxydiester **22**, which is the 'O-analogue' of **20**, yielded neither the 7-membered dilactone, nor the 14-membered tetralactone, but only the known trimer **23** and tetramer **24** of 2,2-dimethylpropiolactone (*Scheme 7*).

[1]) B. Iliev, A. Linden, H. Heimgartner, *Helv. Chim. Acta* **2003,** *86*, 3215.

1. Introduction

The continuous and current interest in cyclic depsipeptides is a result of their well known biological activity. A large number of them have been isolated from natural sources, mainly from marine or surface cultures of the corresponding microorganisms *(cf*. [1-8]). Typical examples are the antibiotics valinomycin [9-11] and the enniatins [12], which act as ionophores [13]. The most demanding step in the synthesis of such compounds is the cyclization. As they contain amide groups and at least one ester group in the core, the cyclic depsipeptides could be prepared by the formation of either the amide or ester bonds as the ring closure step.

The cyclization *via* amide-bond formation (lactamization; *e.g*. [14-16]) is usually carried out by following protocols for the synthesis of cyclopeptides using coupling reagents. On the other hand, successful cyclizations *via* ester-bond formation (lactonization; *e.g*. [17-19]) have also been described. In the last few years, the number of reports on the use of macrolactonizations in the preparation of cyclodepsipeptides has increased remarkably [6-8][20][21]. A useful method for the ring closure of depsipeptides which contain α,α–disubstituted α–amino acids is the so-called 'direct amide cyclization' method, developed in our laboratory [22-28]. The basic concept is that an amide of type **1** in a toluene solution or suspension is treated with dry HCl gas. Cyclization by elimination of the corresponding ammonium chloride leads to the intermediate 1,3-oxazol-5(4*H*)-one of type **2**. In the absence of other nucleophiles, the oxazolone undergoes a ring enlargement *via* intramolecular nucleophilic attack of the hydroxyl group at the carbonyl C-atom of the neighboring lactone group, leading to the depsipeptide **3** (*Scheme 1).*



Scheme 1

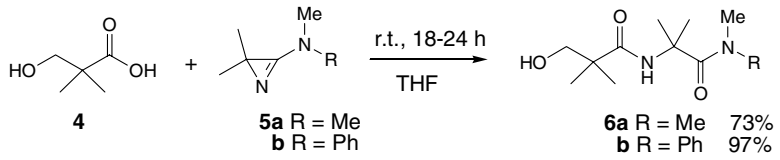
As was reported earlier, this method has been used efficiently for the synthesis of morpholine-2,5-diones (*i.e*. 6-membered cyclic depsipeptides) [23][29] as well as for some 9-, 12-, 15-[23],

16-[27] and 19-membered rings [30]. For the preparation of the 6-, 9-, 12- and 15- membered rings of type **3**, the linear precursors **1** have been prepared by coupling α–hydroxy acids with 2*H*-azirin-3-amines, whereas β–hydroxy acids and 2*H*-azirin-3-amines led to the precursors of the 16- and 19-membered cyclodepsipeptides. The azirines themselves have been a target of our studies for some years [31-36], mainly because they proved to be useful synthons for α,α-disubstituted α-amino acids in peptide synthesis [31][33][34][37-40].

Because the reaction of α–hydroxy acids with 2*H*-azirin-3-amines followed by the 'direct amide cyclization' proved to be a convenient access to morpholine-2,5-diones, we intended to generalize this reaction sequence. Therefore, we carried out the reaction under similar conditions with some β–hydroxy acids in order to obtain 7-membered cyclic depsipeptides. In the present paper, we report the results of the reaction of 2*H*-azirin-3-amines with 3-hydroxy-2,2-dimethylpropanoic acid (**4**).

2. Results and Discussion

2.1. Direct Amid Cyclization. As a model β–hydroxy acid we chose 3-hydroxy-2,2-dimethylpropanoic acid (**4**), mainly due to its commercial availability and its previous use in this type of reactions [26][27]. The linear dipeptides **6** were prepared by the standard procedure [26] of coupling **4** with the corresponding *2H*-azirin-3-amine (**5a** or **5b;** *cf*. [31] and refs. cit. therein), to yield **6a** and **6b**, respectively, in excellent yields and without side products (*Scheme 2)*.

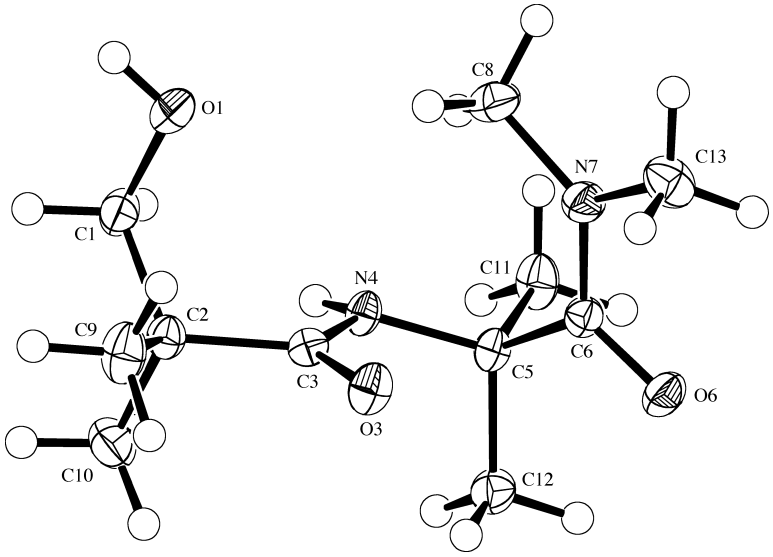


4 **5a** R = Me **6a** R = Me 73%
b R = Ph **b** R = Ph 97%

Scheme 2

Although the general protocol proposed MeCN as a solvent [26], THF turned out to be a better solvent in this particular case. In addition to the spectroscopic characterization of **6a** and **6b** (*cf.* [27]), their structures were established by X-ray crystallography (*Fig. 1*).

a)



b)

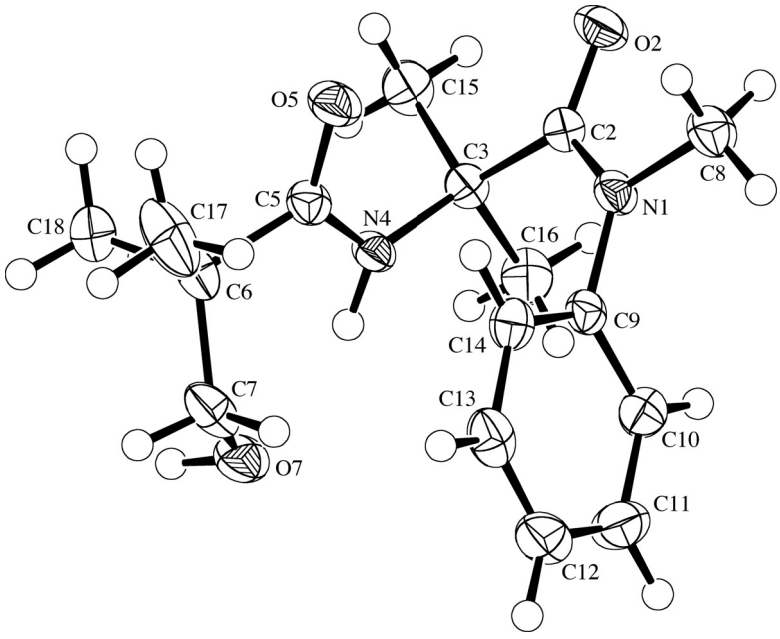


Fig. 1. ORTEP-Plots [41] *of the molecular structures of* a) **6a** *and* b) *one of the two symmetry-independent molecules of* **6b** (arbitrary numbering of the atoms; 50% probability ellipsoids).

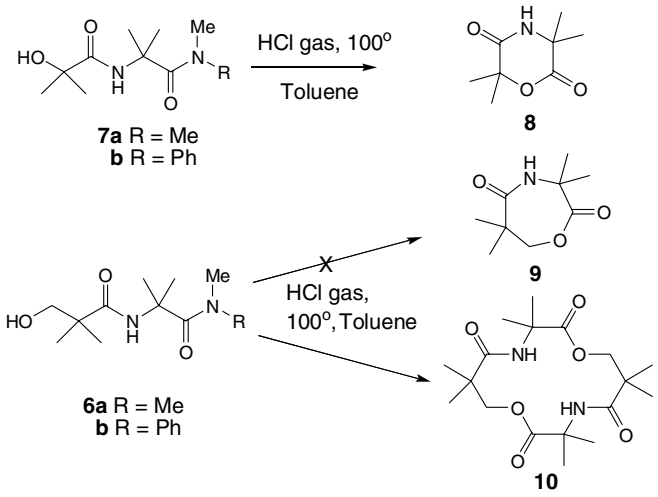
The conformations of the backbones of **6a** and **6b** are very similar, with the exception of the orientation of the OH group. In **6a**, the NH group forms an intermolecular H-bond with its

adjacent amide O-atom from a neighboring molecule (N(4)···O(6") 2.885(1) Å; N(4)-H···O(6") 161(1)^{o}). This interaction links the molecules into extended chains which run parallel to the *y*-axis and have a graph set motif [42] of C(5). The OH group forms an intermolecular H-bond with its adjacent amide O-atom from a different neighboring molecule (O(1)···O(3') 2.770(2) Å; O(1)-H···O(3') 169(2)^{o}) and thereby also links the molecules into infinite chains which run parallel to the *y*-axis and have a graph set motif of C(6). The combination of the intermolecular interactions links the molecules into a two-dimensional network which runs parallel to the *xy*-plane.

In the case of **6b**, there are two symmetry-independent molecules in the asymmetric unit and they have almost identical conformations. The NH group in each molecule forms an intramolecular H-bond with the OH group (*e.g.* N(4)···O(7) 2.728(2) Å; N(4)-H···O(7) 142(1)^{o} in molecule A) to yield a six-membered loop with a graph set motif of S(6). The OH group of molecule A forms an intermolecular H-bond with the primary amide O-atom of molecule B (O(7)···O(25') 2.684(1) Å; O(7)-H···O(25') 173(2)^{o}), while the OH group of molecule B has a similar interaction with a different molecule A (O(27)···O(5") 2.692(1) Å; O(27)-H···O(5") 174(2)^{o}). These interactions link the molecules into infinite chains in which both symmetry-independent molecules are incorporated in an alternating ···A···B···A···B··· sequence. These chains run parallel to the *y*-axis and have a binary graph set motif of $C_2^2(12)$.

The dipeptide **6b**, was subjected to the reaction conditions of the 'direct amide cycliszation', *i.e*. dry HCl gas was bubbled through a toluene suspension of **6b** at 100^{o}. It was expected that **6b** would react in an analogous manner to the amide **7**, which gave 3,3,6,6-tetramethylmorpholine-2,5-dione (**8**) in up to 60% yield [43] (*Scheme 3*). Surprisingly, only the dimer of the expected 7-membered ring **9**, namely the 14-membered 3,3,6,6,10,10,13,13-octamethyl-1,8-dioxa-4,11-diazacyclotetradecane-2,5,9,12-tetraone (**10**), was formed in 72% yield (*Scheme 3*).

The ^{1}H-NMR spectrum of **10** showed no signal for OH groups and confirmed the presence of NH groups. Two singlets for Me groups and a singlet for CH_2 were also clearly distinguished. The ^{13}C-NMR spectra showed the presence of two C=O groups (174.3 and 178.2 ppm in (D_6)DMSO), which was further confirmed by the IR spectrum (KBr; 1723 and 1673 cm^{-1}).



Scheme 3

Furthermore, the ^{13}C-NMR spectrum indicated two different types of Me_2C groups, in addition to a OCH_2 group. With this set of data, the distinction between the monomeric lactone **9** and the dimer **10** was not possible. But the mass spectra (CI and ESI mode) indicated a molecular weight of 370, which corresponds to the 14-membered depsipeptide **10**. Finally its structure was confirmed by X-ray crystallography (*Fig. 2*).

The molecule sits across a crystallographic center of inversion. The symmetry-unique NH group forms a very weak intermolecular H-bond with the amide O-atom from the same amide group of an adjacent molecule (N(4)···O(5') 3.483(2) Å; N(4)-H···O(5') 170°). This interaction links the molecules into extended chains which run parallel to the *z*-axis and have a graph set motif of C(4). The other amide group in the molecule participates in an identical intermolecular interaction of necessity because of the centrosymmetric nature of the molecule. The chains thereby formed also run parallel to the *z*-axis but in the opposite direction. The molecules themselves bridge adjacent chains, so that the combination of both interactions links the molecules into two-dimensional networks which lie parallel to the (100) plane. The cross-linking of the chains also builds H-bonded loops involving four molecules and yields the graph set motif of $R_4^4(26)$.

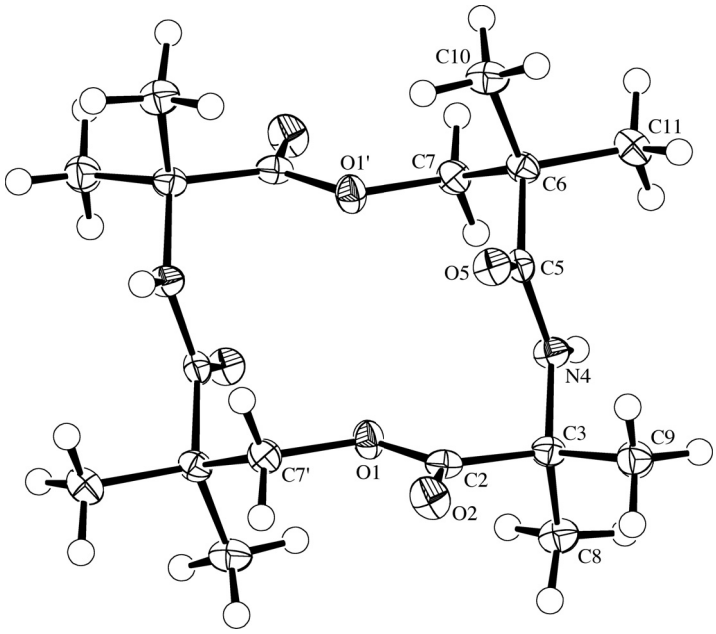


Fig. 2. ORTEP-Plot [41] *of the molecular structure of* **10** (arbitrary numbering of the atoms; 50% probability ellipsoids).

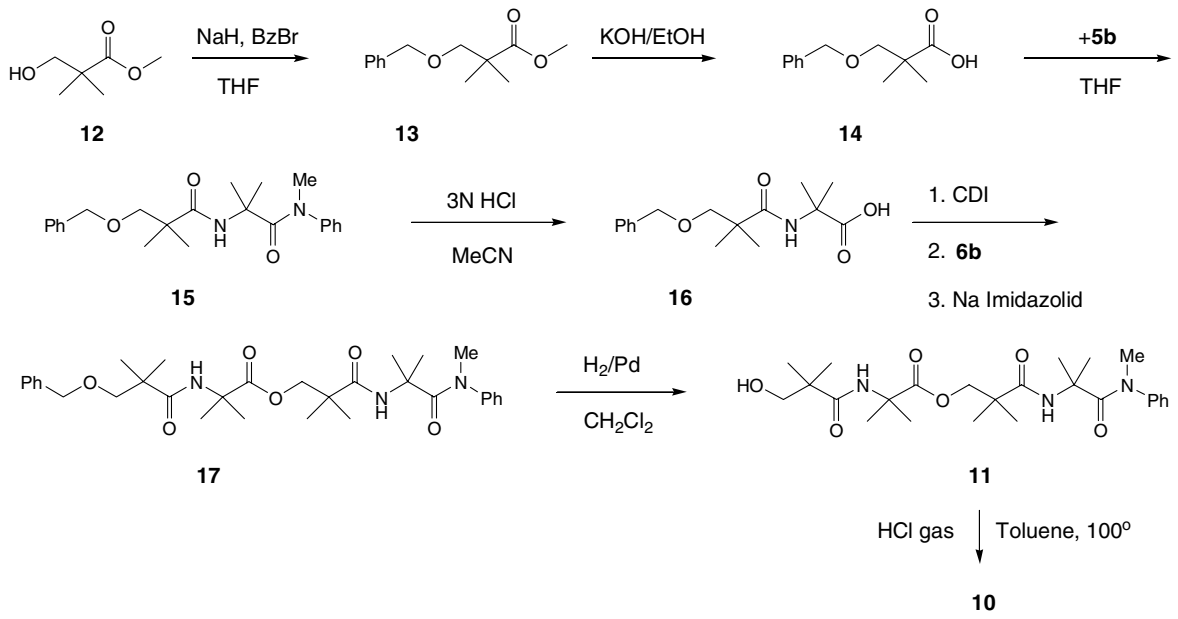
With the aim of obtaining the 7-membered, monomeric cyclodepsipeptide **9** (*Scheme 3)*, we repeated the reaction with varying concentrations of the starting material **6b** and different reaction times. However, under all conditions **10** was formed as the only product, although in variable yield. Thus, the maximum yield of 72% was obtained at a concentration of 20 mM, whereas with a concentration of 2 mM the yield dropped to 35%, and at a concentration of 40 mM the yield was only 61%.

The rate determining step of the 'direct amide cyclization' is believed to be the formation of the oxazolone ring (see *Scheme 1*), a process favored by the precipitation of the corresponding ammonium salt. Thus the formation of the lactone is a function of the salt's solubility in toluene[2)]. As a result, *N*,*N*-dimethylamides of type **6a** should react more easily than *N*-methyl-*N*-

[2)] It has been shown previously, that the formation of a 16-membered cyclic depsipeptide, which in toluene (heterogeneous conditions) was obtained in 60% yield, does not occur in homogeneous solution in DMF [26].

phenylamides like **6b** under the conditions of the 'direct amide cyclization', because the initially formed $Me_2NH.HCl$ is less soluble in toluene than Ph(Me)NH.HCl.
Therefore, we also used **6a** as a starting material. The cyclization with HCl gas in toluene at 100° gave again the product **10**. The lower yield (32%) is mainly caused by purification difficulties (see experimental part).

In order to prepare **10** by a specific synthesis, we synthesized the open chain precursor, the linear depsipeptide **11**, according to standard procedures, starting from the commercially available methyl ester **12**. After protection of the OH group by benzylation to give **13** and deprotection of the carboxyl group, the intermediate **14** was coupled with **5b** to yield the diamide **15.** The product of its acid-catalyzed hydrolysis **16** was coupled with **6b** to give **17**, which after deprotection gave **11** in a total yield of 24% *(Scheme4)*.



Scheme 4

Crystallization from a mixture of CH_2Cl_2, i-PrOH, and hexane gave crystals, which were suitable for an X-ray crystal-structure determination (*Fig. 3*).

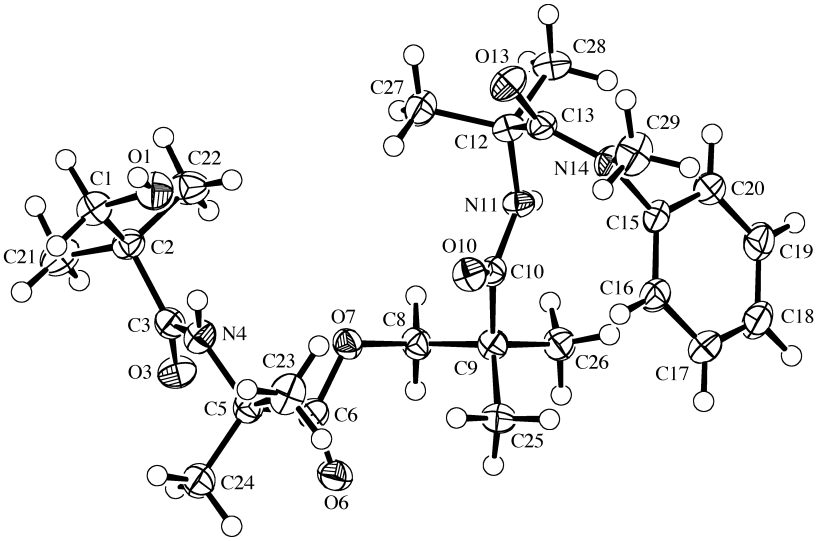


Fig. 3. ORTEP-Plot [41] *of the molecular structure* of **11** (arbitrary numbering of the atoms; 50% probability ellipsoids).

Although the molecule is achiral, the crystal structure is chiral. The absolute structure has not been determined and was defined arbitrarily. The amide NH group closest to the OH group forms an intramolecular H-bond hydroxy O-atom (N(4)···O(1) 2.709(3) Å; N(4)-H···O(1) 135(3)^{o}). This gives rise to a six-membered loop with a graph set motif of S(6), analogous to compound **6b** (*Fig. 1*). The other amide group forms an intermolecular H-bond with the adjacent amide O-atom from a neighboring molecule (N(11)···O(13'') 2.932(3) Å; N(11)-H···O(13'') 155(3)^{o}). This interaction links the molecules into infinite chains which run parallel to the *y*-axis and have a graph set motif of C(5). The OH group forms an intermolecular H-bond with its adjacent amide O-atom from a different neighboring molecule (O(1)···O(3') 2.655(3) Å; O(1)-H···O(3') 158(4)^{o}) and thereby also links the molecules into infinite chains which run parallel to the *y*-axis and have a graph set motif of C(6). The combination of intermolecular interactions links the molecules into a two-dimensional network which runs parallel to the *yz*-plane.

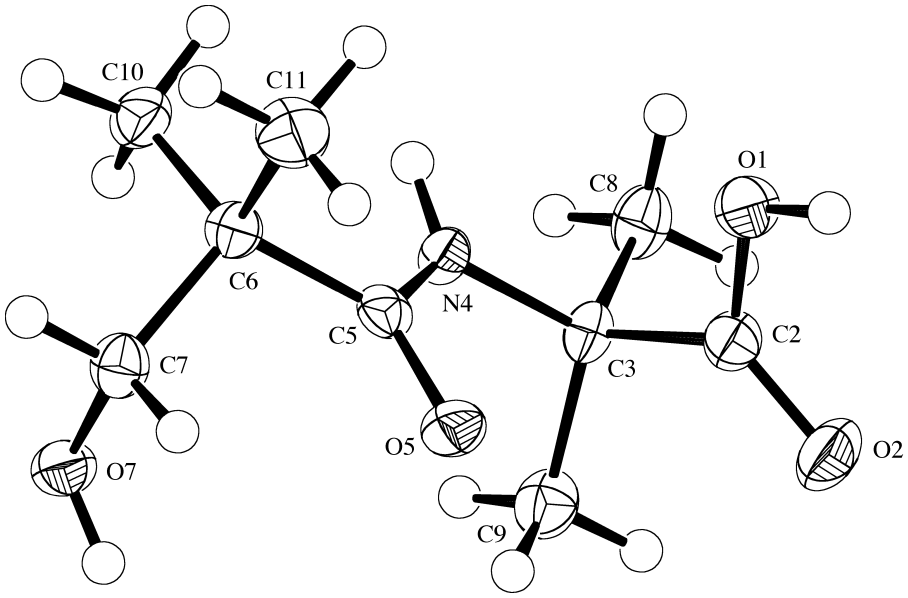
Compound **11** was subjected to cyclization under the standard conditions of the 'direct amide cyclization'. Once more, the 14-membered cyclodepsipeptide **10** was the only product that could be isolated, with the moderate yield of 42%.

2.2. Other lactonisation methods. - After all attempts to obtain the 7-membered ring **9** by the 'direct amide cyclization' failed, even after a ten-fold dilution of the reaction mixture, we were faced with a number of classical lactonisation options, starting mainly with the corresponding hydroxy acid **18**, which was obtained easily from either of the amides **6** by hydrolysis in an acidic medium. The crystal-structure of **18** is shown in *Fig. 4*.

The NH group forms an intermolecular H-bond with the O-atom of the hydroxy group of a neighboring molecule (N(4)···O(7''') 3.086(2) Å; N(4)-H···O(7''') 165(2)^{o}). This interaction links the molecules into extended chains which run parallel to the *y*-axis and have a graph set motif of C(6). The OH group forms an intermolecular H-bond with C=O of the COOH group from a different neighboring molecule (O(7)···O(2'') 2.746(2) Å; O(7)-H···O(2'') 170(2)^{o}). This interaction also links the molecules into infinite chains which run parallel to the *y*-axis and have a graph set motif of C(9). The OH group of COOH forms an intermolecular H-bond with the amide O-atom of a third neighboring molecule (O(1)···O(5') 2.606(2) Å; O(1)-H···O(5') 172(2)^{o}). Again, this interaction links the molecules into infinite chains which run parallel to the *y*-axis and have a graph set motif of C(7). The combination of all H-bonding interactions links the molecules into two-dimensional network which lies parallel to the *xy*-plane.

The variety of lactonization methods is enormous, and we could try only a few of them. As starting point, we used the review by *Nicolaou* [44] where the classical methods of *Yamaguchi* [45], *Corey-Nicolaou* [46], and *Mukaiyama* [47] are mentioned. Unfortunately, none of the above reactions yielded the desired product, and the only products obtained were the activated acid derivates, namely the *Yamaguchi* mixed anhydride and the *Corey* active ester, respectively. Some modern variations of these methods [48] were also tried, but they failed to give the desired product too.

a)



b)

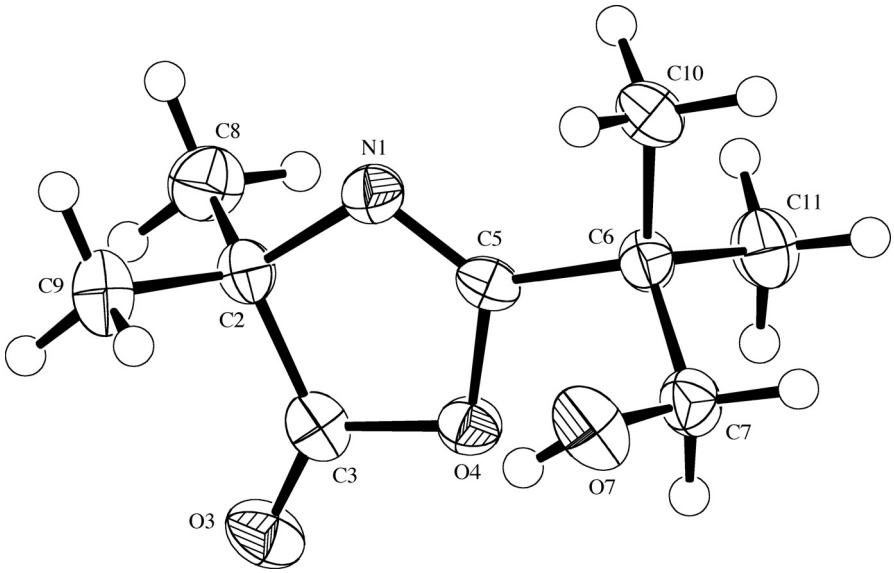
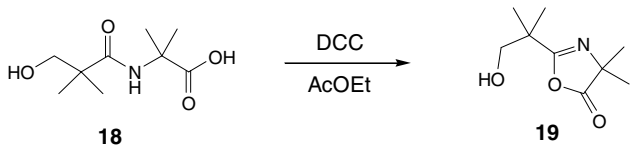


Fig. 4. ORTEP-Plots [41] *of the molecular structures of* a) **18** *and* b) *one of the two symmetry-independent molecules of* **19** (arbitrary numbering of the atoms; 50% probability ellipsoids).

The most common cyclization methods, using DCC or its water-soluble derivatives and analogues, gave as the only product 2-(2-hydroxy-1,1-dimethylethyl)-4,4-dimethyloxazol-5(4*H)*-one (**19**) in 36% yield (*Scheme* 5). This is the postulated intermediate of the prospected 'direct

amide cyclization' **6→9.** Even after addition of 4-(dimethylamino)pyridine (DMAP) to a mixture of **18** and DCC, a procedure known to be suitable for the synthesis of medium sized lactones [49], the reaction path did not change and **19** was isolated as the only product, although in moderate yield.



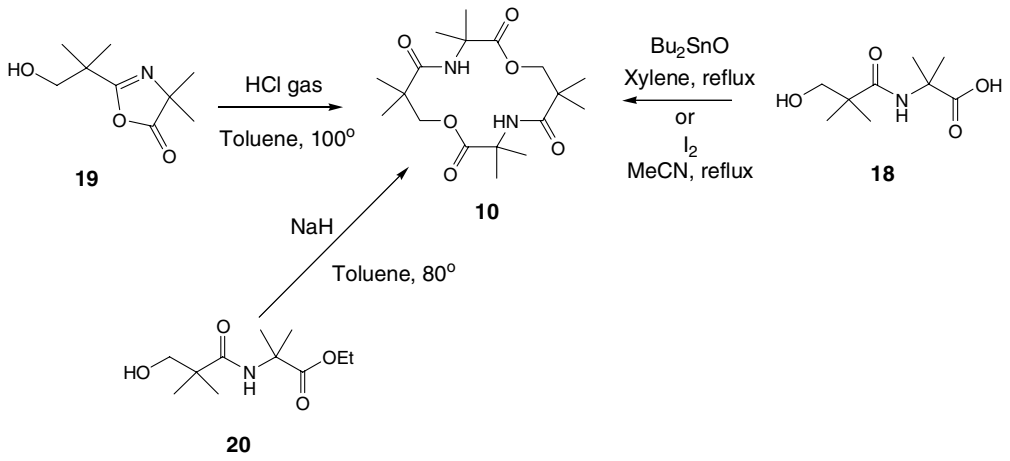
18 **19**

Scheme 5

In general, 1,3-oxazol-5(4*H*)-ones are reactive species; in the case of **19**, the *gem*-dimethyl group seems to stabilize it, so that it could be isolated in crystalline form. In the IR spectrum (KBr), **19** showed a characteristic strong C=O absorption at 1836 cm^{-1} and in the ^{13}C-NMR spectrum, the singlets for C=O and C=N appeared at 182.8 and 166.6 ppm, respectively. The structure of **19** was established by X-ray crystallography (*Fig. 4)*.

The asymmetric unit contains two symmetry-independent molecules, whose conformations differ only in the orientation of the OH group. The OH group of molecule A forms an intermolecular H-bond with the N-atom of molecule B (O(7)···N(21') 2.891(2) Å; O(7)-H···N(21') 159(3)^{o}). In turn, molecule B has an identical interaction with another molecule A. These interactions link the molecules into extended ···A···B···A···B··· chains which run parallel to the *y*-axis and have a graph set motif [42] of $C_2^2(12)$.

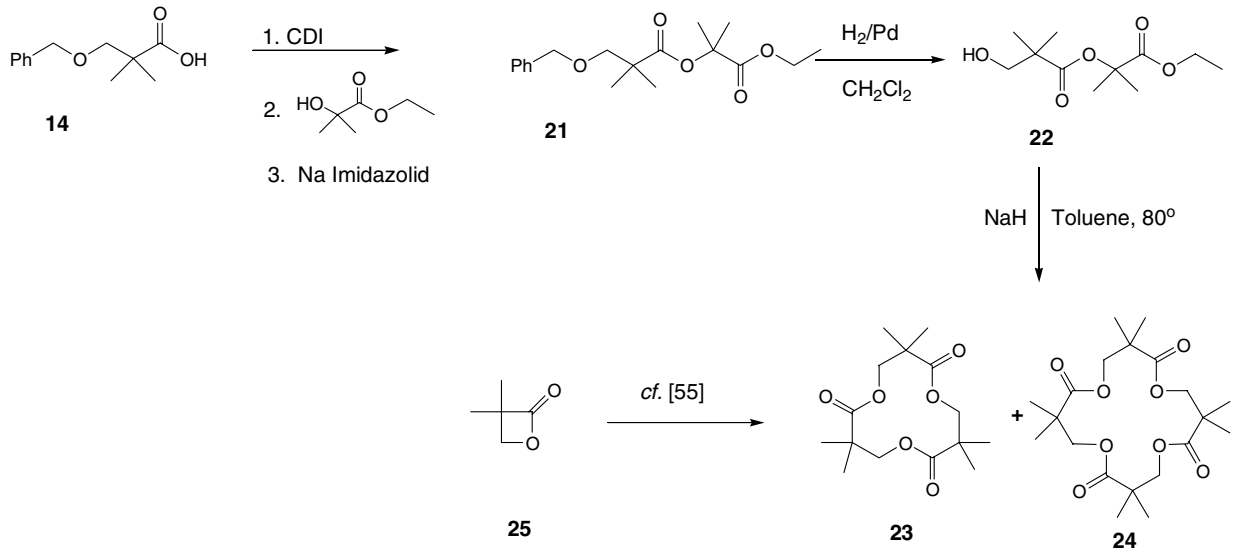
As **19** is expected to be the intermediate in the 'direct amide cyclization' **6→9,** we attempted to transform **19** to the depsipeptide in polar, aprotic solvents (AcOEt, MeCN), but all attempts failed. After two days of heating **19** under reflux, only the starting material was isolated. Another way of converting **19** to the depsipeptide **9** was the 'direct amide cyclization'. This reaction yielded again only product **10** in excellent yield (86%, *Scheme 6*).



Scheme 6

The next step we took on the way to the synthesis of the 7-membered **9** was to try out some reactions involving salts of metals, such as Sb [50], Sn [51], Ag [52], Sc [53] and Ru [54], known to catalyze the formation of small and medium sized lactones. Most of these attempts failed in the case of **18,** and only few led to a definite product, namely once more the dimeric cyclodepsipeptide **10** (*Scheme* 6). Surprisingly, the reaction with I_2 in boiling MeCN, which was initially used to cyclize terpene-like hydroxy acids [55], gave again the 14-membered ring **10** in moderate yield (*Scheme* 6). Recently, *Richard et al.* have reported the synthesis of 7-membered lactones, containing an amino group in their basic structure, by treatment of the corresponding hydroxy esters with NaH in a toluene suspension [56]. Therefore, we treated the ester **20** under the same conditions. To our disappointment, this reaction yielded again the dimeric compound **10** as the sole product.

The discrepancy between the reactions of 6-hydroxy-4-azahexanoic esters [56] and **6** is very surprising. One of the possible reasons for the failure of this method in the case of **6** could lie in the presence of the amide bond and its rigidity. With the aim of proving this hypothesis, the ester analogue of the amide **6**, *i.e*. the diester **22**, was synthesized in the same way as compound **11** (*Scheme* 7).



Scheme 7

Subjecting compound **22** to the reaction conditions described in [56] led to a mixture of products, among which the tri- and tetralactones **23** and **24** were isolated as the main products. None of the expected 7-membered dilactone could be detected. As an additional product, 2-hydroxyisobutyric acid was also obtained. The structures of **23** and **24**, *i.e.* the cyclic tri- and tetramers of 3-hydroxy-2,2-dimethylpropanoic acid (**4**) were confirmed by X-ray crystal-structure analyses (*Fig. 5*). It turned out that these compounds are already known and the crystal structure of **24** has been published previously [57]. They have been prepared by oligomerisation of 3-hydroxy-2,2-dimethylpropionolactone **25**. Therefore, we propose that in the reaction of **22** with NaH, **25** is formed by the intramolecular nucleophilic attack of the OH group at the central ester group and cleavage of this ester. Then, **25** undergoes the oligomerisation. Apparently, the alternative nucleophilic attack at the terminal ester group of **22**, which would lead to the 7-membered dilactone, cannot compete with the formation of the β-lactone.

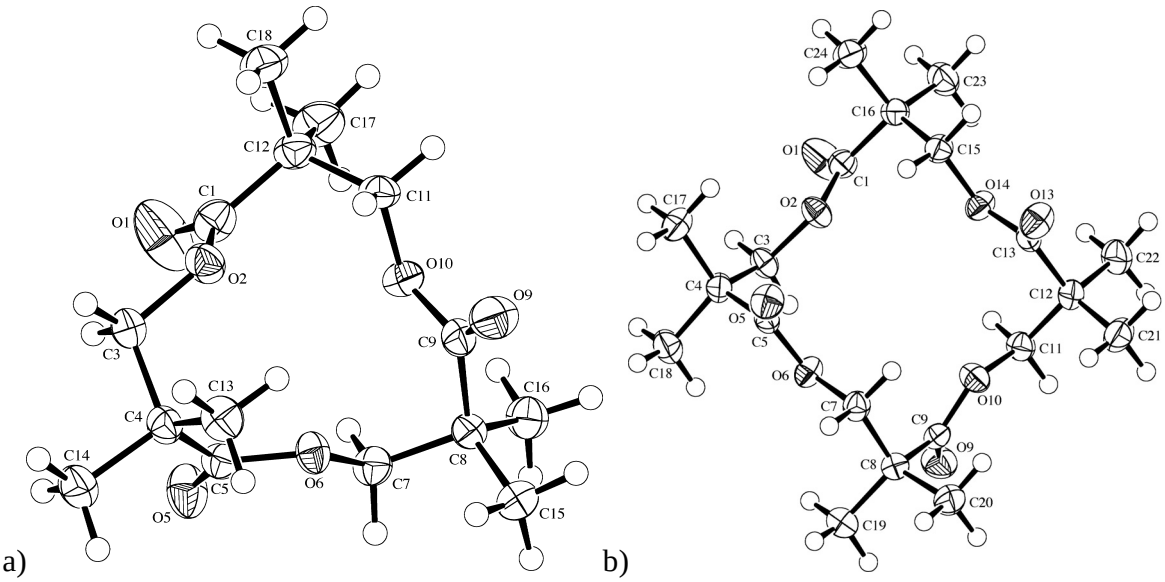


Fig. 5. ORTEP-Plots [41] *of the molecular structures of* a) *one of the two symmetry-independent molecules of* **23** *and* b) **24** (arbitrary numbering of the atoms; 50% probability ellipsoids).

3. Conclusions

In conclusion, our attempts to prepare the 7-membered cyclic depsipeptide 3,3,6,6-tetramethyl-1-oxa-4-azacycloheptane-2,5-dione (**9**) using the 'direct amide cyclization' starting with 3-hydroxy-2,2-dimethyl-*N*-[1-methyl-1-(*N*-methyl-*N*-phenylcarbamoyl)ethyl]-propanamide (**6b**) failed. The only product obtained was the dimeric 14-membered cyclodepsipeptide **10**, which was formed in a very good yield. Furthermore, the attempts to prepare the monomeric lactone **9** using various classical lactonisation procedures failed too, and in almost all cases **10** was obtained as the main product in yields of 28-72%. Five different methods for the synthesis of **10** were developed. Despite all the variations in reaction conditions and the knowledge of the crystal structures of the starting materials and some of the intermediates, there is no convincing explanation for this unexpected result and additional experiments are required.

We thank the analytical units of our institute for spectra and analysis, and the *Swiss National Science Fondation* and *F. Hoffmann-La Roche AG*, Basel, for financial support.

Experimental Part

1. General. Thin-layer chromatography (TLC): *Merck* TLC aluminium sheets, silica gel *60* F_{254}. Prep. TLC: *Merck* PLC plates (glass), silica gel *60* F_{254}, 2 mm and 40-63 μm. Flash chromatography (CC): *Uetikon-Chemie* 'Chromatographiegel' *C-560*. M.p.: *Büchi 540* apparatus, uncorrected. IR Spectra: *Perkin-Elmer Spectrum one* spectrometer; in KBr, unless otherwise stated, absorption bands in cm^{-1}. ^{1}H-NMR (300 MHz) and ^{13}C-NMR (75.5 MHz) spectra: *Bruker ARX-300* instrument; in $CDCl_3$ at 300 K; TMS as internal standard, unless otherwise stated; δ in ppm, coupling constants *J* in Hz. HSQC and HMBC spectra: *Bruker DRX-600* instrument; ^{1}H-NMR (600 MHz) and ^{13}C-NMR (150 MHz). Mass spectrometry (MS): *Finnigan MAT-90* for electron impact ionization (EI), *Finnigan SSQ-700* for chemical ionization (CI, with NH_3) and electrospray ionization (ESI, in MeOH + Na), unless otherwise stated.

2. *Starting materials.* 2,2,*N*,*N*-Tetramethyl-*N*-phenyl-2*H*-azirin-3-amine (**5a**) and 2,2,*N*-trimethyl-*N*-phenyl-2*H*-azirin-3-amine (**5b**) were prepared according to standard procedures (*cf.* [31] and refs. cited therein). All other products used were commercially available.

3. *Coupling with 2*H*-Azirin-3-amines.*

N-*[1-(Dimethylcarbamoyl)-1-methylethyl]-3-hydroxy-2,2-dimethylpropanamide* (**6a**). To a soln. of 3-hydroxy-2,2-dimethylpropanoic acid (**4**; 806 mg, 6.84 mmol) in dry THF (5ml), **5a** (1.231 g, 7.52 mmol) was added dropwise. The mixture was stirred at r.t. for 36 h, the solvent was evaporated, and the remaining solid was purified by CC (SiO_2, MeOH/CH_2Cl_2 1:10) and dried in h.v. Yield: 1.200 g (76%) of **6a**. Pale yellow crystals. M.p. 126.2-127.4°. ^{1}H-NMR: 1.10, 1.33 (2*s*, 2 *Me*$_2$C); 3.22 (*s*, Me_2N); 3.46 (*s*, CH_2O); 3.90 (br. *s*, OH); 6.79 (br. *s*, NH). ^{13}C-NMR: 22.1, 26.3 (2*q*, 2 *Me*$_2$C); 41.6 (*s*, Me$_2$*C*); 42.4 (*q*, Me_2N); 58.7 (*s*, Me$_2$*C*); 70.4 (*t*, CH_2O); 174.1, 177.2 (2*s*, 2 CO). CI-MS: 231 (68, $[M + 1]^+$), 186 (100).

3-Hydroxy-2,2-dimethyl-N-*[1-methyl-1-(*N-*methyl*-N-*phenylcarbamoyl)ethyl]propanamide* (**6b**). To a soln. of **4** (806 mg, 6.84 mmol) in dry THF (5ml), **5b** (1.309 g, 7.52 mmol) was added dropwise. The mixture was stirred at r.t. for 24 h, the solvent was evaporated and the remaining solid was purified by CC (SiO_2, MeOH/CH_2Cl_2 1:20) and dried in h.v. Yield: 1.86 g (93%) of **6b**.

White solid. M.p.102.8-103.3° ([27]: 103.4-104°). ^{1}H-NMR: 1.11, 1.38 (2*s*, 2 *Me*$_2$C); 3.28 (*s*, MeN); 3.44 (*s*, CH_2O); 3.90 (br. *s*, OH); 6.77 (br. *s*, NH); 7.25-7.45 (*m*, 5 arom. H). ^{13}C-NMR: 22.2, 26.3 (2*q*, 2 *Me*$_2$C); 41.6 (*s*, Me$_2$*C*); 43.6 (*q*, MeN); 58.7 (*s*, Me$_2$*C*); 70.4 (*t*, CH_2O); 128.2 (*d*, 1 arom. CH); 128.4, 129.5 (2*d*, 4 arom. CH); 144.4 (*s*, 1 arom. C); 174.1, 177.2 (*2s*, 2 CO).

4. *Cyclizations to 3,3,6,6,10,10,13,13-Octamethyl-1,8-dioxa-4,11-diazacyclotetradecane-2,5,9,12-tetraone* (**10**).

4.1. *Direct Amide Cyclisations. Procedure A.* A suspension of **6b** (584 mg, 2 mmol) in dry toluene (100 ml) was heated to 100°, and HCl gas was bubbled through the suspension for 7 min. Then, the mixture was let to cool to r.t. while bubbling N_2 through it (*ca*. 20 min). The solvent was evaporated, the white residue was washed with 3 × 15 ml of CH_2Cl_2 and dried in h.v. Yield: 267 mg (72%) of **10**. White powder. M.p. 299.2-300.4°. IR: 3393v*s* (NH), 2990*s*, 2977*s*, 2935*m*, 1723v*s* (C=O), 1673v*s* (C=O), 1523v*s*, 1171v*s* (C-O). ^{1}H-NMR ((D$_7$)DMF): 1.12, 1.40 (2*s*, 2 *Me*$_2$C each); 4.00 (*s*, 2 CH_2O); 7.64 (*s*, 2 NH). ^{13}C-NMR ((D$_7$)DMF): 22.1, 24.6 (2*q*, 2 *Me*$_2$C each); 41.6, 55.4 (2*s*, 2 Me$_2$*C*); 71.3 (*t*, CH_2O); 174.3 (*s*, C=O). ^{13}C-NMR ((D$_6$)DMSO): 20.9, 23.2 (2*q*, 2 *Me*$_2$C each); 40.4, 54.4 (2*s*, 2 Me$_2$*C*); 70.1 (*t*, CH_2O); 173.0, 174.3 (*s*, C=O). CI-MS: 388 (34, $[M + NH_4]^+$), 371 (100, $[M + 1]^+$). ESI-MS: 393 (100, $[M + Na]^+$). Anal. calc. for $C_{18}H_{30}N_2O_6$ (370.45): C 58.36, H 8.16, N 7.56; found C 57.94, H 8.18, N 7.47.

Procedure B. A suspension of **6a** (230 mg, 1 mmol) in dry toluene (50 ml) was heated to 100°, and HCl gas was bubbled through the suspension for 3 min. Then, the mixture was let to cool to r.t. while bubbling N_2 through it (*ca*.20 min). The solvent was evaporated, the white residue was washed with 3 × 10 ml of CH_2Cl_2 and the remaining solid was recrystallized from MeCN to yield 60 mg (32%) of **10.**

Procedure C. A suspension of **11** (see *section 5*, 477 mg, 1 mmol) in dry toluene (50 ml) was heated to 100°, and HCl gas was bubbled through the suspension for 3 min. Workup as described in *Procedure A* gave 92 mg (49%) of **10.**

4.2 *Other lactonisation methods. 2-[(3-Hydroxy-2,2-dimethyl-propanoyl)amino]-2-methyl-propanoic acid* (**18**). To a soln. of **6b** (2.00 g, 7.35 mmol) in THF (10 ml), 3N HCl (10 ml) was added dropwise at 0° under constant stirring. After 8 h at r.t., THF was removed i.v. and the H_2O phase was extracted with AcOEt (5 × 20 ml). The combined org. fractions were dried ($MgSO_4$) and the solvent evaporated. The remaining brownish crystals were washed twice with

Et_2O/PrOH 100:1. Yield: 1.312g (92%) of **18**. White crystals. M.p.142.3-143.4° ([27]: 142.8-144.0°). ^{1}H-NMR ((D_6)DMSO): 1.00, 1.35 (2*s*, 2 *Me*$_2$C); 3.36 (*s*, CH_2O); 5.00 (br. *s*, OH); 7.52 (br. *s*, NH); 12.12 (br. *s*, COOH).

Procedure D. A soln. of **18** (205 mg, 1 mmol) and I_2 (15 mg, 0.06 mmol) in dry MeCN (15 ml) was heated to reflux for 3 d. After evaporation of the solvent, the residue was washed with 5% $Na_2S_2O_3$ soln. and extracted with AcOEt, and the combined org. fractions were dried ($MgSO_4$). Purification by CC yielded 89 mg (49%) of **10** as a white powder.

Procedure E. A soln. of **18** (103 mg, 0.5 mmol) and Bu_2SnO (25 mg, 0.1 mmol) in dry xylene (25 ml) was heated under reflux for 2 d in a *Dean-Stark* apparatus (N_2 -atmosphere). Then, the solvent was evaporated i.v., the solid residue was washed with Et_2O (2 × 10 ml) and than with warm acetone (5 × 10 ml). The acetone fraction was concentrated to 5 ml, cooled and filtered to yield 36 mg (38%) of **10.**

Ethyl 2-[(3-Hydroxy-2,2-dimethylpropanoyl)amino]-2-methylpropanoate (**20**). A soln. of **6b** (584 mg, 2 mmol) in a 10% EtOH soln. in toluene (110 ml) was heated to 100°, and HCl gas was bubbled through the suspension for 7 min. Then, the mixture was let to cool to r.t. while bubbling N_2 through it (*ca*. 20 min). The solvent was evaporated, purification by CC (CH_2Cl_2/acetone 100:1) yielded 397 mg (86%) of **20** as colorless oil. ^{1}H-NMR: 1.14 (*s*, *Me*$_2$C); 1.28 (*t*, *Me*CH_2O); 1.43 (*s*, *Me*$_2$C); 3.53 (*d*, CH_2OH); 4.05 (*q*, MeC*H*$_2$O); 6.79 (*s*, NH). ^{13}C-NMR: 15.6 (*q*, Me); 22.1, 26.3 (2*q*, 2 *Me*$_2$C); 41.6 (*s*, Me$_2$*C*); 61.4 (*t*, *C*H_2O); 69.1 (*t*, *C*H_2O); 76.8 (s, Me$_2$*C*); 174.3, 178.6 (2*s*, 2 CO). ESI-MS: 254 (100, $[M + Na]^+$).

Procedure F. To a soln. of **20** (232 mg, 1 mmol) in dry toluene (5 ml), NaH (40 mg of a 60% suspension in mineral oil, 1 mmol) was added slowly at 0° and under constant stirring (N_2 -atmosphere). After 4.5 h at 80°, the mixture was acidified with 0.1 N HCl (~6 ml) to pH 5 and extracted with CH_2Cl_2 and AcOEt. The combined org. fractions were dried ($MgSO_4$) and evaporated i.v. The crystalline residue was washed with CH_2Cl_2 to yield 52 mg (28%) of **10**.

*5. Synthesis of 2-Methyl-2-{[1-methyl-1-(*N*-methyl*-N*-phenylcarbamoyl)ethyl]carbamoyl}-propyl 2-[(3-Hydroxy-2,2-dimethyl-propanoyl)amino]-2-methylpropanoate* (**11**).

Methyl 3-Benzyloxy-2,2-dimethylpropanoate (**13**). To a suspension of NaH (440 mg of a 60% suspension in mineral oil, 11 mmol) in dry THF (15 ml) methyl 3-hydroxy-2,2-dimethylpropanoate (1.322 g, 10 mmol) was added dropwise at 0° and under constant stirring.

The reaction was stirred at r.t. for 1 h, then benzyl bromide (1.710 g, 10 mmol) was added. After heating under reflux for 3 h, the mixture was cooled, washed with brine (2 × 25ml), the brine fractions were extracted with AcOEt and the combined org. fractions were dried ($MgSO_4$). Purification by CC (SiO_2 , hexane/Et_2O 10:1) yielded 1.05 g (47%) of **13**. Colorless oil. IR (film): 2976*m*, 2863*m*, 1736*vs* (C=O), 1475*s*, 1454*s*, 1363*m*, 1308*s*, 1226*s*, 1192*s*, 1152*s* (C-O), 1100*s* (C-O), 1029*m*, 738*m*, 698*m*. ^{1}H-NMR: 1.37 (*s*, *Me*$_2$C); 3.62 (*s*, CH_2O); 3.84 (*s*, MeO); 4.68 (*s*, $PhCH_2$); 7.40-7.52 (*m*, 5 arom. H). ^{13}C-NMR: 22.4 (*q*, *Me*$_2$C); 43.6 (*t*, CH_2); 51.7 (*s*, Me$_2$*C*); 73.1 (*q*, MeO); 76.9 (*t*, Ph*C*H_2); 127.3, 127.6, 128.2 (3*d*, 5 arom. CH); 138.4 (*s*, 1 arom. C); 176.8 (*s*, C=O). EI-MS: 222 (28, $M^{+\cdot}$), 116 (26), 107 (20), 101 (20), 91 (100), 65 (8).

3-Benzyloxy-2,2-dimethylpropanoic acid (**14**). To a soln. of of **13** (1.00 g, 4.5 mmol) in EtOH (20 ml), 8 ml of 2N KOH were added at 0^o . After 1 h stirring at r.t., the org. solvent was evaporated i.v., the remaining soln. was acidified with 1N HCl to pH 1 and extracted with Et_2O. The org. fractions were dried ($MgSO_4$) and evaporated i.v. The residue was recrystallized from hexane. Yield: 830 mg (88%) of **14**. White crystals. M.p. 62.1-63.8^o. IR: 2975*m*, 2861*m*, 1707*vs* (C=O), 1454*s*, 1364*m*, 1163*w*, 1100*s* (C-O), 738*m*, 698*m*. ^{1}H-NMR ((D$_6$)DMSO): 1.07 (*s*, *Me*$_2$C); 3.42 (*s*, CH_2O); 4.49 (*s*, $PhCH_2$); 7.25-7.42 (*m*, 5 arom. H); 12.21 (*s*, COOH). ^{13}C-NMR ((D$_6$)DMSO): 22.2 (*q*, *Me*$_2$C); 40.6 (*s*, Me$_2$*C*); 72.3 (*t*, CH_2O); 76.7 ($PhCH_2$); 127.2, 127.3, 128.1 (3*d*, 5 arom. CH); 138.4 (*s*, 1 arom. C); 177.3 (*s*, COOH). EI-MS: 208 (7, $M^{+\cdot}$), 107 (49), 91 (100), 79 (9), 65 (9).

3-Benzyloxy-2,2-dimethyl-N-*[1-methyl-1-(*N-*methyl*-N-*phenylcarbamoyl)ethyl]propanamide* (**15**). To a soln. of **14** (800 mg, 3.85 mmol) in THF (10 ml), a soln. of **5b** (670 mg, 3.85 mmol) in THF (2 ml) was added dropwise. After 24 h, the solvent was removed i.v. and the residue was purified by CC (CH_2Cl_2/MeOH 40:1). Yield: 1.230 g (84%) of **15**. White solid. M.p.105.6-106.8^o. IR: 3339*vs* (NH), 2992*m*, 2956*m*, 2838*m*, 1644*vs* (C=O), 1593*m*, 1253*s*, 1103*s* (C-O), 976*w*, 753*m*, 713*m*, 618*w*. ^{1}H-NMR: 0.98, 1.31 (2*s*, 2 *Me*$_2$C); 3.08 (*s*, CH_2O); 3.14 (*s*, MeN); 4.31 (*s*, $PhCH_2$); 6.96 (*s*, NH), 7.12-7.27 (*m*, 10 arom. H). ^{13}C-NMR: 22.8, 26.4 (2*q*, 2 *Me*$_2$C); 41.2 (*q*, MeN); 42.5, 57.4 (2*s*, *2* Me$_2$*C*); 73.3 (*t*, CH_2O); 76.4 (*t*, $PhCH_2$); 127.4, 127.5, 127.7, 127.9, 128.3, 129.1 (6*d*, 10 arom. CH); 137.6, 145.1 (2*s*, 2 arom. C); 173.2, 175.2 (2*s*, 2 C=O). ESI-MS: 405 (100, $[M + Na]^+$).

2-[(3-Benzyloxy-2,2-dimethylpropanoyl)amino]-2-methylpropanoic acid (**16**). To a soln. of **15** (1.200 g 3.14 mmol) in THF (5 ml), 3N HCl (5 ml) was added dropwise at 0^o. The mixture was

left overnight at r.t., the org. solvent was evaporated i.v., and the residue was extracted with AcOEt. The combined org. fractions were washed with brine and dried ($MgSO_4$). After evaporation, the crystals were washed with Et_2O/hexane 2:1. Yield: 818 mg (89%). White crystals. M.p.109.4-110.2°. IR: 3355*vs* (OH), 2989-2863*s* (br.), 1717*vs* (C=O), 1620*vs* (C=O), 1533*vs*, 1468*s*, 1397*s*, 1257*s*, 1162*s*, 1162*s*, 1092*vs*, 1012*m*, 930*m*, 8289*s*, 753*s*, 704*m*, 693*m*. ^{1}H-NMR: 1.17, 1.46 (2*s*, 2 *Me*$_2$C); 3.44 (*s*, CH_2O); 4.56 (*s*, $PhCH_2$); 7.31-7.39 (*m*, 5 arom. H, NH). ^{13}C-NMR: 22.8, 24.8 (2*q*, 2 *Me*$_2$C); 42.5, 56.6 (2*s*, 2 Me$_2$*C*); 73.6 (*t*, CH_2O); 76.4 (*t*, $PhCH_2$); 127.6, 127.9, 128.4 (*3d*, 5 arom. CH); 137.2 (*s*, 1 arom. C); 177.2, 178.0 (2*s*, 2 C=O). CI-MS: 294 (100, $[M + 1]^+$), 295(18).

*2-Methyl-2-{[1-methyl-1-(*N-*methyl*-N-*phenylcarbamoyl)ethyl]carbamoyl}propyl 2-[(3-Benzyloxy-2,2-dimethylpropanoyl)amino]-2-methylpropanoate* (**17**). To a soln. of **16** (1.00 g, 3.41 mmol) in dry THF (15 ml), 1,1'-carbonyldiimidazol (CDI; 552 mg, 3.41 mmol) was added. After 2 h stirring at r.t., **6b** (934 mg, 3.41 mmol) was added, followed by the dropwise addition of a Na-imidazolid suspension (73 mg imidazol, 45 mg of a 60% NaH suspension in mineral oil and 3 ml of THF). After stirring overnight, the org. solvent was removed i.v. and the residue was purified by CC (CH_2Cl_2/acetone 60:1). Yield: 1.276g (66%) of **17**. White solid. M.p. 114.2-115.8°. IR: 3353*s* (NH), 2980*m*, 2934*m*, 2873*m*, 1739*vs* (C=O), 1702*m*, 1664*vs* (br., C=O), 1594*s*, 1520*s*, 1494*m*, 1454*m*, 1385*m*, 1382*m*, 1150*vs* (C-O), 1091*m*, 1023*m*, 923*m*, 904*m*, 738*m*, 705*m*. ^{1}H-NMR: 1.13, 1.14 (2*s*, 2 *Me*$_2$C); 1.44 (*s*, 2 *Me*$_2$C); 3.27 (*s*, MeN); 3.42 (*s*, CH_2OH); 4.03 (*s*, CH_2O); 4.57 (*s*, $PhCH_2$); 7.04 (*s*, NH); 7.21-7.41 (*m*, 10 arom. H, NH). ^{13}C-NMR: 22.3, 22.9, 24.7, 25.2 (4*q*, 4 *Me*$_2$C); 41.4 (*q*, MeN); 42.5, 42.7, 55.8, 58.3 (4*s*, 4 Me$_2$*C*); 70.9 (*t*, CH_2O); 73.5 (*t*, CH_2O); 76.6 ($PhCH_2$); 127.5, 127.7, 128.0, 128.3, 128.3, 129.3 (6*d*, 10 arom. H); 137.6, 144.3 (2*s*, 2 arom. C); 173.6, 173.7, 174.0, 175.8 (4*s*, 4 C=O). CI-MS: 590 (100, $[M + Na]^+$).

2-Methyl-2-{[1-methyl-1-(N-methyl-N-phenylcarbamoyl)ethy]lcarbamoyl}propyl 2-[(3-Hydroxy-2,2-dimethylpropanoyl)amino]-2-methylpropanoate (**11**). To a soln. of **17** (1.200 g, 2.11 mmol) in dry CH_2Cl_2 (15 ml), 150 mg of Pd/C were added and the mixture was stirred under an H_2-atmosphere at r.t. overnight. The suspension was filtered over celite, and evaporated i.v. The product was used without further purification. Yield: 901mg (89%) of **11**. White crystals. M.p. 139.2-140.3°. IR: 3358*vs* (OH), 3281*m*, 2981*m*, 2886*m*, 1746*vs* (C=O), 1664*vs*, 1623*vs*, 1592*s*, 1533*vs*, 1382*s*, 1264*s*, 1224*m*, 1144*vs*, 1140*m*, 1062*m*, 1024*w*, 781*m*, 708*s*. ^{1}H-NMR ((D$_6$)DMSO): 0.99, 1.04, 1.31, 1.38 (4*s*, 4 *Me*$_2$C); 3.20 (*s*, MeN); 3.34 (*d*, ^3J = 6, CH_2O); 3.91 (*s*,

CH_2O); 4.97 (*t*, ^3J = 6, OH); 7.16-7.28 (*m*, 2 arom. H, NH); 7.30-7.40 (*m*, 3 arom. H); 7.58 (*s*, NH). ^{13}C-NMR ((D_6)DMSO): 21.9, 22.1, 24.6, 25.9 (4*q*, 4 *Me*$_2$C); 41.6, 42.6, 54.8, 56.4 (4*s*, 4 Me$_2$*C*); 67.5, 69.9 (2*t*, 2 CH_2O); 126.3, 127.0, 128.7 (3*d*, 5 arom. CH); 137.8 (*s*, 1 arom. C); 172.3, 173.6, 173.7, 175.61 (4*s*, 4 C=O). ESI-MS: 500 (100, $[M + Na]^+$).

6. *Formation of 2-(2-Hydroxy-1,1-dimethylethyl)-4,4-dimethyloxazol-5(4*H*)-one* (**19**).

Procedure F. A soln. of **18** (103 mg, 0.5 mmol) and *N*,*N'*-dicyclohexylcarbodiimide (DCC; 104 mg, 0.5 mmol) in AcOEt (10 ml) was stirred overnight at r.t., then filtered, washed with AcOEt, and the solvent was evaporated i.v. Recrystallisation of the residue from MeCN yielded 33mg (36%) of **19** as white crystals. M.p. 128.1-128.8°. IR: 3327v*s* (OH), 2928v*s*, 2850v*s*, 1836v*s*, 1626v*s*, 1574v*s*, 1536v*s*, 1436*m*, 1311*s*, 1271*m*, 1243*s*, 1088*s*, 1045*m*, 892*m*, 641*s*. ^{1}H-NMR ((D_6)DMSO): 1.13, 1.30 (2*s*, 2 *Me*$_2$C); 3.41 (*d*, ^3J = 6, CH_2OH); 4.91 (*t*, ^3J = 6, OH). ^{13}C-NMR ((D_6)DMSO): 21.3, 24.2 (2*q*, 2 Me$_2$*C*); 64.9, 67.4 (2*s*, 2 Me$_2$*C*); 166.6 (*s*, C=N); 181.8 (*s*, C=O). CI-MS: 204 (100, $[M + NH_4]^+$), 186 (30, $[M + 1]^+$), 174 (10), 158 (6).

Procedure G. A soln. of **18** (103 mg, 0.5 mmol) and 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (86 mg, 0.5 mmol) in AcOEt (10 ml) was stirred overnight at r.t., then washed with brine and extracted with AcOEt. The combined org. fractions were dried ($MgSO_4$), the solvent was evaporated i.v., and the residue purified by CC (CH_2Cl_2/acetone 150:1). Yield: 26mg (28%) of **19**.

Procedure H. A soln. of **18** (103 mg, 0.5 mmol) and 4-(dimethylamino)pyridine (DMAP; 66 mg, 0.5 mmol) in CH_2Cl_2 (10 ml) was stirred for 15 min at r.t. Then, DCC (103 mg, 0.5 mmol) was added. The mixture was left overnight, then filtered, washed with AcOEt, and the solvent was evaporated i.v. Purification by CC (CH_2Cl_2/acetone 150:1) yielded 42 mg (45%) of **19.**

7. *Synthesis and Cyclization of 1-Ethoxycarbonyl-1-methylethyl 3-Hydroxy-2,2-dimetylpropanoate.*

1-Ethoxycarbonyl-1-methylethyl 3-Benzyloxy-2,2-dimethylpropanoate (**21**). To a soln. of **14** (1.00 g, 3.41 mmol) in dry THF (15 ml), CDI (552 mg, 3.41 mmol) was added and the mixture was stirred at r.t. for 2 h. Then, methyl 2-hydroxy-2,2-dimethylethanoate (450 mg, 3.41 mmol) was added followed by the dropwise addition of 3 ml of a Na-imidazolid suspension (73 mg imidazole, 45 mg of a 60% NaH suspension in mineral oil and 3 ml THF). After stirring

overnight, the org. solvent was removed i.v. and the residue purified by CC (CH_2Cl_2/acetone 100:1). Yield: 780 mg (48%) of **21.** Colorless oil. IR (film): 2983*m*, 1743v*s* (C=O), 1471*w*, 1383*w*, 1293*m*, 1179*s* (C-O), 1130*s* (C-O), 1028*m*, 738*w*, 698*w*. ^{1}H-NMR: 1.21 (*s* + *t*, *Me*$_2$C, *Me*CH_2O); 1.52 (*s*, *Me*$_2$C); 3.47 (*s*, CH_2O); 3.76 (*q*, MeCH_2O); 4.52 (*s*, PhCH_2); 7.25-7.32 (*m*, 5 arom. H). ^{13}C-NMR: 13.9 (*q*, Me); 22.2, 24.3 (2*q*, 2 *Me*$_2$C); 43.4 (*s*, Me$_2$*C*); 60.9 (*t*, MeCH_2O); 73.2 (*t*, CH_2O); 76.7 (*t*, PhCH_2); 77.9 (*s*, Me$_2$*C*); 127.2, 127.3, 128.1 (3*d*, 5 arom. CH); 138.5 (*s*, 1 arom. CH); 172.5, 175.1 (2*s*, 2 C=O). ESI-MS: 345 (100, [*M* + Na]$^+$).

1-Ethoxycarbonyl-1-methylethyl 3-Hydroxy-2,2-dimethylpropanoate (**22**). To a soln. of **19** (900 mg, 2.61 mmol) in dry CH_2Cl_2 (15 ml), 120 mg of Pd/C were added and the mixture was stirred under H_2-atmosphere at r.t. overnight. The suspension was filtered over celite, and evaporated i.v. The product was used without further purification. Yield: 777 mg (91%) of **22**. Colorless oil. IR (film): 3528*w* (br.), 2885*m*, 2939*m*, 1743v*s* (C=O), 1474*m*, 1296*s*, 1180*m* (C-O), 1128*s* (C-O), 1053*m*, 882*w*, 758*w*, 670*w*. ^{1}H-NMR: 1.11 (*s*, *Me*$_2$C); 1.22 (*t*, *Me*CH_2O); 1.53 (2*s*, 2 *Me*$_2$C); 3.53 (*d*, CH_2OH); 4.13 (*q*, MeCH_2O). ^{13}C-NMR: 13.8 (*q*, Me); 21.5, 24.4 (2*q*, 2 *Me*$_2$C); 44.3 (*s*, Me$_2$*C*); 61.3 (*t*, MeCH_2O); 70.0 (*t*, CH_2O); 78.5 (*s*, Me$_2$*C*); 172.6, 176.1 (2*s*, 2 C=O). ESI-MS: 255 (100, [M + Na]$^+$).

3,3,7,7,11,11-Hexamethyl-1,5,9-trioxacyclododecane-2,6,10-trione (**23**) and *3,3,7,7,11,11,15,15-Octamethyl-1,5,9,13-tetraoxacyclohexadecane-2,6,10,14-tetraone* (**24**). To a soln. of **22** (232 mg, 1 mmol) in dry toluene (5 ml), NaH (40 mg of a 60% suspension in mineral oil, 1 mmol) was added slowly at 0^o and under constant stirring (N_2 -atmosphere). After 5 h at 80^o, the mixture was acidified with 0.1 N HCl (~6 ml) to pH 5 and extracted with CH_2Cl_2 . The combined org. fractions were dried ($MgSO_4$) and evaporated i.v. The crystalline residue was purified by CC (CH_2Cl_2/acetone 200:1) to yield 24 mg (8%) of **23.** M.p. [57]and 38 mg (9.5%) of **24**[57].

8. X-ray Crystal-Structure Determination of **6a, 6b, 10, 11, 18, 19,** *and* **23** (*Table* and *Figs. 1-5*)[3)]. All measurements were made on a *Nonius KappaCCD* diffractometer [58] using graphite-

[3]) CCDC- 210670-210676 contain supplementary crystallographic data for this paper. These data can be obtained free of charge *via* www.ccdc.cam.ac.uk/conts/retrieving.html (or form the *Cambridge Crystallographic Data Centre*, 12 Union Road, Cambridge CB12 1EZ, U.K. (fax : +44-(0)1223-336033; e-mail: deposit@ccdc.cam.ac.uk))

monochromated MoK_α radiation (λ 0.71073 Å) and an *Oxford Cryosystems Cryostream 700* cooler. The data collection and refinement parameters are given in the *Table* and views of the molecules are shown in *Figs. 1-5*. Data reductions were performed with *HKL Denzo* and *Scalepack* [59]. The intensities were corrected for *Lorenz* and polarization effects, but not for absorption. The structures were solved by direct methods using SIR92 [60], which revealed the positions of all non-H atoms. There were two symmetry-independent molecules in the asymmetric unit of **6b, 19** and **23**. In each case the atomic coordinates of the two molecules were tested carefully for a relationship from a higher symmetry space group using the program PLATON [61], but none could be found. The non-hydrogen atoms were refined anisotropically. Except for **10**, the amide and hydroxy H-atoms in the structures were placed in the positions indicated by difference electron density maps and their positions were allowed to refine together with individual isotropic displacement parameters. All remaining H-atoms in all structures were placed in geometrically calculated positions and each was assigned a fixed isotropic displacement parameter with a value equal to 1.2U_{eq} of its parent atom (1.5U_{eq} for the Me groups of **6a**, **11**, **19** and **23**). For **6b**, **10** and **18**, each structure was refined on F using full-matrix least-squares procedures, which minimized the function $\Sigma w(|F_o| - |F_c|)^2$. Refinement of the remaining structures was carried out on F^2 by minimizing the corresponding function based on F^2. Corrections for secondary extinction were applied with the exception of **18**. In **6b**, **10**, **11**, **18** and **23**, six, two, one, three and three reflections, respectively, were omitted from the final refinement of each structure because their observed intensities were much lower than the calculated values as a result of being partially obscured by the beam stop. Neutral atom scattering factors for non-H atoms were taken form [62a] and the scattering factors for H-atoms were taken from [63]. Anomalous dispersion effects were included in F_c [64]; the values for f' and f'' were those of [62b]. The values of the mass attenuation coefficients are those of [62c]. All calculations were performed using the *teXsan* crystallographic software package [65] for **6b, 10,** and **18** and the *SHELXL97* program [66] for **6a, 11, 19,** and **23,** respectively.

Table Crystallographic Data of Compounds **6a, 6b, 10, 11, 18, 19** and **23**

	6a	**6b**	**10**
Recrystallized from	$CDCl_3$/AcOEt /acetone	toluene/CH_2Cl_2 /AcOEt	$CDCl_3$/MeOH
Empirical formula	$C_{11}H_{22}N_2O_3$	$C_{16}H_{24}N_2O_3$	$C_{18}H_{30}N_2O_6$
Formula weight [g mol^{-1}]	230.31	292.38	370.44
Crystal color, habit	yellow, prism	colorless, prism	colorless, prism
Crystal dimensions [mm]	$0.12 \times 0.20 \times 0.25$	$0.18 \times 0.20 \times 0.25$	$0.10 \times 0.12 \times 0.20$
Temp.[K]	160(1)	160(1)	160(1)
Crystal system	monoclinic	triclinic	monoclinic
Space group	$P2_1/c$	$P\bar{1}$	$P2_1/c$
Z	4	4	2
Reflections for cell determination	3944	9546	2273
2θ range for cell determination [°]	4–60	2–60	4–55
Unit cell parameters a[Å]	8.6612(1)	8.9268(1)	9.1635(2)
b [Å]	10.4339(2)	11.9930(1)	9.6501(2)
c [Å]	14.4276(2)	16.4091(2)	10.8786(3)
α [°]	90	99.0727(5)	90
β [°]	100.5340(6)	92.8174(5)	103.3648(8)
γ [°]	90	108.5531(6)	90
V [$Å^3$]	1281.85(3)	1635.33(3)	935.93(4)
D_X [g cm^{-3}]	1.193	1.187	1.314
$\mu(MoK_\alpha)$ [mm^{-1}]	0.0863	0.0820	0.0981
Scan type	ϕ and ω	ϕ and ω	ϕ and ω
2θ(max) [°]	60	60	55
Total reflections measured	36257	68555	21539
Symmetry independent reflections	3749	9576	2140
Reflections with $I > 2\sigma(I)$	3038	6579	1713
Reflections used in refinement	3749	6579	1713
Parameters refined	160	396	119
R [on$F$; $I > 2\sigma(I)$ reflections]	0.0432	0.0500	0.0412
wR [on$F$; $I > 2\sigma(I)$ reflections]	-	0.0496	0.0447
wR [onF^2; all indept. reflections]	0.1204	-	-
Weighting parameter [p][a)]	-	0.005	0.005
Weighting parameters [a; b][b)]	0.0527; 0.3914	-	-
Goodness of fit	1.046	2.870	2.901
Secondary extinction coefficient	0.029(5)	$2.7(3) \times 10^{-6}$	$3.9(8) \times 10^{-6}$
Final Δ_{max}/σ	0.001	0.0004	0.0004
$\Delta\rho$ (max; min) [e $Å^{-3}$]	0.34; -0.36	0.28; -0.22	0.25; -0.20

a) $w^{-1} = \sigma^2(F_o) + (pF_o)^2$

b) $w^{-1} = \sigma^2(F_o^2) + (aP)^2 + bP]$ where $P = (F_o^2 + 2F_c^2)/3$

11	**18**	**19**	**23**
CH_2Cl_2/*i*-PrOH/hexane	toluene/acetone/ *i*-PrOH	MeCN/acetone/ CH_2Cl_2	CH_2Cl_2/ acetone
$C_{25}H_{39}N_3O_6$	$C_9H_{17}NO_4$	$C_9H_{15}NO_3$	$C_{15}H_{24}O_6$
477.60	203.24	185.22	300.35
colorless, prism	yellow, plate	colorless, prism	colorless, plate
$0.10 \times 0.12 \times 0.20$	$0.02 \times 0.15 \times 0.17$	$0.15 \times 0.15 \times 0.25$	$0.02 \times 0.18 \times 0.23$
160(1)	160(1)	160(1)	160(1)
monoclinic	monoclinic	monoclinic	monoclinic
$P2_1$	$P2_1/n$	$P2_1/c$)	$P2_1/c$
2	4	8	8
3173	2004	3721	5976
4-55	4–50	4–50	4–50
9.3227(2)	8.2708(2)	11.7684(5)	9.8304(1)
11.1213(2)	8.2429(2)	10.5276(4)	11.9228(2)
12.8333(3)	15.7690(4)	16.1536(8)	27.7139(5)
90	90	90	90
99.6690(9)	98.9548(9)	90.464(2)	97.1582(6)
90	90	90	90
1311.66(5)	1061.95(5)	2001.3(2)	3222.92(9)
1.209	1.271	1.229	1.238
0.0861	0.0992	0.0918	0.0948
ϕ and ω	ω	ϕ and ω	ϕ and ω
55	50	50	50
32002	14054	30962	51446
3177	1859	3521	5680
2118	1330	2425	3981
3176	1330	3521	5677
329	139	252	392
0.0410	0.0411	0.0570	0.0436
-	0.0379	-	-
0.0965	-	0.1556	0.1120
-	0.005	-	-
0.0436; 0	-	0.0585; 0.9613	0.0552; 0.1627
0.995	1.865	1.090	1.037
0.025(3)	-	0.011(2)	0.0036(6)
0.001	0.0002	0.001	0.001
0.18; -0.19	0.18; -0.21	0.22; -0.22	0.20; -0.21

REFERENCES

[1] H. Vervoort, W. Fenical, R. de Epifanio, *J. Org. Chem.* **2000,** *65,* 782.

[2] N. Sitachitta, R. T. Williamson, W. H. Gerwick, *J. Nat. Prod*. **2000**, *63,* 197.

[3] F. D. Horgan, D. B. de los Santos, G. Goetz, B. Sakamoto, Y. Kan, H. Nagai, P. J. Scheuer, *J. Nat. Prod*. **2000,** *63,* 152.

[4] K. Fujii, K. Sivinen, E. Naganawa, K. Harada, *Tetrahedron* **2000,** *56,* 725.

[5] B. N. Belofski, P. R. Jensen, W. Fenical, *Tetrahedron Lett.* **1999,** *40,* 2913.

[6] A. K. Gosh, A. Bischoff, *Org. Lett.* **2000,** *2,* 1573.

[7] F. Sarabia, S. Chammaa, F. J. Lopez-Herrera, *Tetrahedron Lett.* **2002**, *43,* 2961.

[8] J. Hong, L. Zhang, *Frontiers of Biotechnology & Pharmaceuticals* **2002,** *3,* 193.

[9] K. Brockmann, G. Schmidt-Kastner, *Chem. Ber*. **1955,** *88,* 57.

[10] M. M. Shemyakin, N. A. Aldanova, R. I. Vinogradova, V. Y. Feigina, *Tetrahedron Lett.* **1963**, *28,* 1921.

[11] B. C. Pressman, E. J. Harris, W. S. Jagger, J. N. Johnson, *Procl. Nat. Acad. Sci. U.S.A.* **1967,** *58,* 1949.

[12] Y. A. Ovchinnikov, V. T. Ivanov, A. V. Evstratov, I. I. Mikhaleva, V. F. Bystrov, S. L. Portnova, T. A. Balashova, E. N. Meshcheryakova, V. M. Tul'chinskii, *Int. J. Pept. Protein Res*. **1974,** *6,* 465.

[13] B. C. Pressman, *Ann. Rev. Biochem.* **1976,** *45,* 501.

[14] A. M. Sefler, M. C. Kozlowski, T. Guo, P. A. Bartlett, *J. Org. Chem.* **1977**, *62,* 93.

[15] Y. L. Dory, J. M. Mellor, J. F. McAleer, *Tetrahedron Lett.* **1996**, *52,* 1343.

[16] T. Imaeda, Y. Hamada, T. Shioiri, *Tetrahedron Lett.* **1994**, *35,* 591.

[17] K. W. Li, J. Wu, W. Xing, J. A. Simpson, *J. Am. Chem. Soc.* **1996,** *118,* 7237.

[18] Y. Hirai, K. Yokota, T. Momose, *Heterocycles* **1994,** *39,* 603.

[19] S. Cerini, E. Gavuzzo, G. Luisi, F. Pinnen, *Int. J. Pept. Protein Res.* **1993,** *41,* 282.

[20] T. K. Chakraboity, S. Ghosh, S. Dutta, *Tetrahedron Lett.* **2001,** *45*, 5085.

[21] M. Eggen, S. K. Nair, G. I. Georg, *Org. Lett.* **2001,** *3,* 1813.

[22] D. Obrecht, H. Heimgartner, *Helv. Chim. Acta* **1984,** *67,* 526.

[23] D. Obrecht, H. Heimgartner, *Helv. Chim. Acta* **1987,** *70,* 329.

[24] D. Obrecht, H. Heimgartner, *Helv. Chim. Acta* **1990,** *73,* 221.

[25] J. M. Villagordo, H. Heimgartner, *Helv. Chim. Acta* **1997,** *80,* 748.

[26] K. N. Koch, A. Linden, H. Heimgartner, *Helv. Chim. Acta* **2000,** *83,* 233.

[27] K. N. Koch, A. Linden, H. Heimgartner, *Tetrahedron* **2001,** *57,* 2311.

[28] H. Heimgartner, F. S. Arnhold, S. Fritschi, K. N. Koch, A. Linden; J. E. F. Magirius, *J. Heterocycl. Chem.* **1999,** *36,* 1539.

[29] A. Linden, F. Ghorbani-Salman Pour, R. A. Breitenmoser, H. Heimgartner, *Acta Cryst., Sect. C* **2001,** *57,* 634.

[30] K. N. Koch, H. Heimgartner, *Helv. Chim. Acta* **2000,** *83,* 1881.

[31] H. Heimgartner, *Angew. Chem., Int. Ed. Engl.* **1991,** *30,* 238.

[32] C. B. Bucher, A. Linden, H. Heimgartner, *Helv. Chim. Acta* **1995,** *78,* 935; C. B. Bucher, H. Heimgartner, *Helv. Chim. Acta* **1996,** *79,* 1903.

[33] R. Luykx, C. B. Bucher, A. Linden, H. Heimgartner, *Helv. Chim. Acta* **1996,** *79,* 527.

[34] G. Suter, S. Stoykova, A. Linden, H. Heimgartner, *Helv. Chim. Acta* **2000,** *83,* 2961.

[35] K. Brun, A. Linden, H. Heimgartner, *Helv. Chim. Acta* **2002,** *85,* 3422; K. Brun, A. Linden, H. Heimgartner, *Helv. Chim. Acta* **2001,** *84,* 1756-1777.

[36] R. A. Breitenmoser, T. Hirt, R. T. N. Luykx, H. Heimgartner, *Helv. Chim. Acta* **2001,** *84,* 972.

[37] P. Wipf, H. Heimgartner *Helv. Chim. Acta* **1990,** *73,* 13.

[38] N. Pradeille, H. Heimgartner *J. Pept. Sci.* **2003,** in press.

[39] W. Altherr, Ph.D. Thesis, Universität Zürich, 1994.

[40] R. T. N. Luykx, Ph.D. Thesis, Universität Zürich, 2000.

[41] C. K. Johnson, 'ORTEP II', Report ORNL-5138, Oak Ridge National Laboratory, Oak Ridge, Tennessee, 1976.

[42] J. Bernstein, R. E. Davis, L. Shimoni, N.-L. Chang, *Angew. Chem. Int. Ed.* **1995,** *34,* 1555.

[43] N. M. Mawad, F. Ghorbani-Salman Pour, A. Linden, H. Heimgartner, in preparation.

[44] K. C. Nicolaou, *Tetrahedron* **1977,** *33*, 683

[45] J. Inanaga, K. Hirata, H. Saeki, T. Katsuki, M. Yamaguchi, *Bull. Chem. Soc. Jpn.* **1976,** *52*, 1989.

[46] E. J. Corey, K. C. Nicolaou, *J. Am. Chem. Soc.* **1974,** *96*, 5614.

[47] T. Mukaiyama, M. Usui, K. Saigo, *Chem. Lett.* **1976,** 49.

[48] M. Hikota, H. Tone, K. Horita, O. Yonemitsu, *J. Org. Chem.* **1990,** *55,* 7.

[49] G. E. Keck, E. P. Boden, M. R. Wiley, *J. Org. Chem.* **1989,** *54*, 896.

[50] Y. Kuroki, K. Ishihara, N. Hanaki, S. Ohara, H. Yamamoto. *Bull. Chem. Soc. Jpn.* **1998,** *71*, 1221.

[51] K. Steliou, A.Szczygielska-Nowosielska, A. Farve, M. A. Poupart, S. Hanessian, *J. Am. Chem. Soc.* **1980,** *102*, 7578.

[52] K. R. Buszek, Y. Jeong, N. Sato, P. C. Still, P. L. Muino, I. Ghosh, *Synth. Commun*. **2001,** *31*, 1781.

[53] K. Ishihara, M. Kubota, H. Kurihara, H. Yamamoto, *J. Am. Chem. Soc.* **1995,** *117*, 4413.

[54] B. M. Trost, J. D. Chisholm, *Org. Lett.* **2002,** *4*, 3743.

[55] T. Fujita, N. Hanyu, T. Mino, M. Sakamoto, *Synthesis* **2001,** *12*, 1846.

[56] S. Richard, G. Prie, A. Guignard, J. Thibonet, J. Luc Parrain, A. Duchene, M. Abarbri, *Helv. Chim. Acta* **2003,** *86*, 726.

[57] A. Matuszowicz, Z. Jedlinski, M. Gawron, Z. Kosturkiewicz, *J. Org. Chem.* **1995**, *60*, 6826.

[58] R. Hooft, *KappaCCD Collect Software*, Nonius BV, Delft, The Netherlands, 1999.

[59] Z. Otwinowski, W. Minor, in 'Methods in Enzymology', Vol. 276, 'Macromolecular Crystallography', part A, Eds. C. W. Carter Jr., R. M. Sweet, Academic Press, New York, 1997, p. 307.

[60] A. Altomare, G. Cascarano, C. Giacovazzo, A. Guagliardi, M. C. Burla, G. Polidori, M. Camalli, SIR92, *J. Appl. Crystallogr.* **1994**, *27*, 435.

[61] A. L. Spek, PLATON, *J. Appl. Crystallogr.* **2003**, *36*, 7.

[62] a) E. N. Maslen, A. G. Fox, M. A. O'Keefe, in 'International Tables for Crystallography', Ed. A. J. C. Wilson, Kluwer Academic Publishers, Dordrecht, 1992 Vol. C, Table 6.1.1.1, p. 477; b) D. C. Creagh, W. J. McAuley, *ibid.* Table 4.2.6.8, p. 219; c) D. C. Creagh, J. H. Hubbell, *ibid.* Table 4.2.4.3, p. 200.

[63] R. F. Steward, E. R. Davidson, W. T. Simpson, *J. Chem. Phys.* **1965**, *42*, 3175.

[64] J. A. Ibers, W. C. Hamilton, *Acta Crystallogr.* **1964,** *17*, 781.

[65] teXsan: Single Crystal Structure Analysis Software, Version 1.10, Molecular Structure Corporation, The Woodlands, Texas, 1999.

[66] G. M. Sheldrick, SHELXL97, Program for the Refinement of Crystal Structures, University of Göttingen, Germany, 1997.

Chapter 2

14-Membered cyclodepsipeptides with alternating β-hydroxy and α-amino acids by cyclodimerization[1])

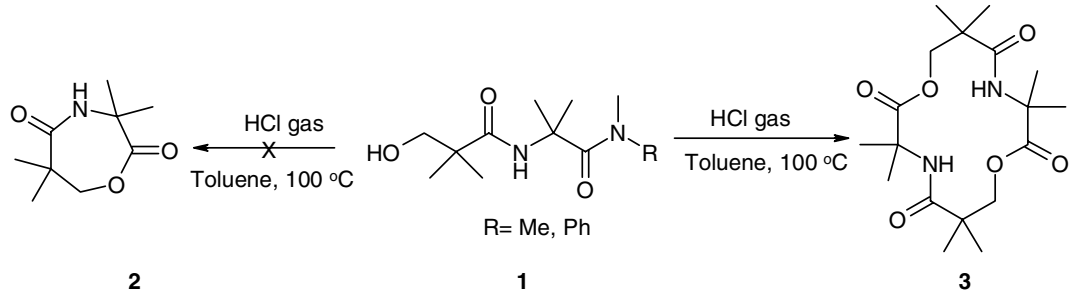
Abstract

The cyclodimerization (twinnig) of β-hydroxy acid amides of type **1** under 'direct amide cyclization' (DAC), conditions is described. Although other coupling methods also gave moderate results, best yields were obtained *via* DAC, reaching 88% for the cyclodimer **10**. In all cases, when starting with racemic material, only the *trans*-substituted cyclodepsipeptides were isolated. Simple molecular modeling revealed that the formation of the cyclodimer is thermodynamically slightly more favorable than that of the cyclomonomer. The proposal that cyclodimer formation is preferred because of the presence of intramolecular H-bonds could not be confirmed by X-ray crystallography. The influence of substituents, both in the amino acid and in the hydroxy acid moieties, was also studied. It is shown, that cyclodimerization was successful only when the hydroxy acid moiety is α,α-disubstituted.

[1]) B. Iliev, A. Linden, R. Kunz, H. Heimgartner, *Tetrahedron*, submitted.

1. Introduction

In a recent paper,[1] we reported that amides **1**, when subjected to the conditions of the 'direct amide cyclization' reaction,[2-9] yielded only the dimerized product **3**. The 14-membered cyclodepsipeptide **3** was isolated as the sole product and none of the expected 7-membered monomer **2** could be detected (Scheme 1).



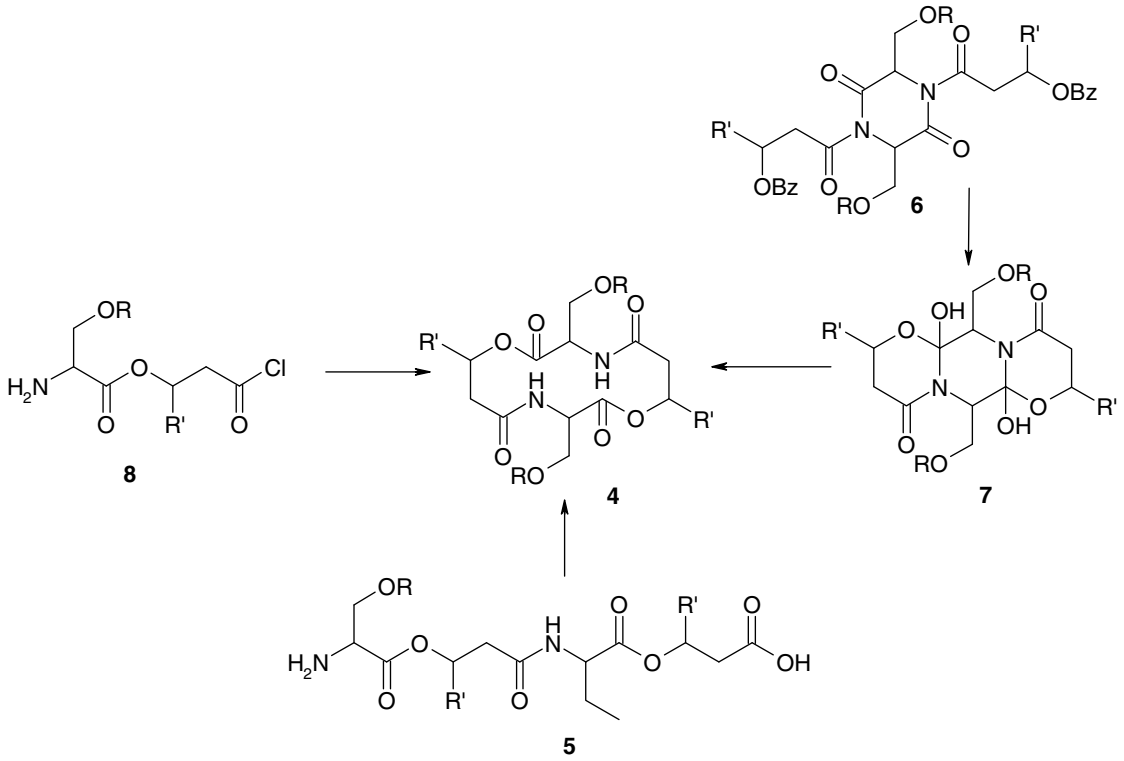
2 **1** **3**

Scheme 1

In order to explain this unexpected result we investigated some other lactonization methods with derivatives of **1**, including that described by *Richard et al.*,[10] which, in the case of ethyl 6-hydroxyhexanoates, had resulted in the formation of 7-membered lactones. Again, in all experiments with derivatives of **1**, where a defined product could be isolated, we obtained only the dimeric product **3.**

Cyclic 14-membered depsipeptides with the same ring skeleton as **3** have been known since the 1960's, and the dimerization process is not as surprising as it seems at first. Since the discovery, isolation and identification of serratamolide (**4**: R = H, R' = $(CH_2)_6CH_3$, Scheme 2) from *Serratia marcescens* in 1961,[11] the proof of its antibiotic activity,[12] and its first total synthesis by *Shemyakin et al.*,[13] the interest in depsipeptides containing β-hydroxy acids has increased significantly, mainly because of their antibiotic properties. The other important biological role of the same compound, is its use as a surface-active agent under the name of serrawettin W1,[14] and it has been patented for the use as a pesticide as well.[15]

The synthetic pathways to serratamolide (**4**) and its derivatives are numerous, but the approaches can be divided into three main groups: classical ring closure of linear precursors, usually by lactam bond formation (**5→4**), ring enlargement (**6→7→4**), and cyclization by twinning (**8→4**) (Scheme 2).



Scheme 2

The main feature of the last-mentioned method is that the cyclization is performed with the monomeric linear precursor, and the twinning, or cyclodimerization, takes place during the course of the reaction. Some basic theories have been offered as an explanation of this dimerization. One of the most popular proposals states that it is mainly due to intermolecular hydrogen bonding between carbonyl and amine groups that are formed during the reaction.[16,17] In the case of **4**, the two planar *trans*-amide groups form a *trans*-annular hydrogen bond (intramolecular) and thus favor the formation of a 14-membered ring. That no monomeric product was formed in the reaction can probably be explained by the fact that such an intramolecular interaction would not be possible within a 7-membered ring. However, the contribution of hydrogen bonding tends to be overestimated as some dimerizations also take place in polar solvents, which could interfere

with such an intramolecular interaction.[17] Another theory proposed by *Ovchinnikov et al*.[18] is that the cyclization is preceded by a linear polycondensation, which results in linear dimers and oligomers, which, under the conditions of high dilution, may undergo cyclization. The extent of the ring closure is determined principally by the most stable conformation of a given linear peptide, being close to that of the cyclic product. On the other hand, the formation of trimers seems to be statistically unfavorable.

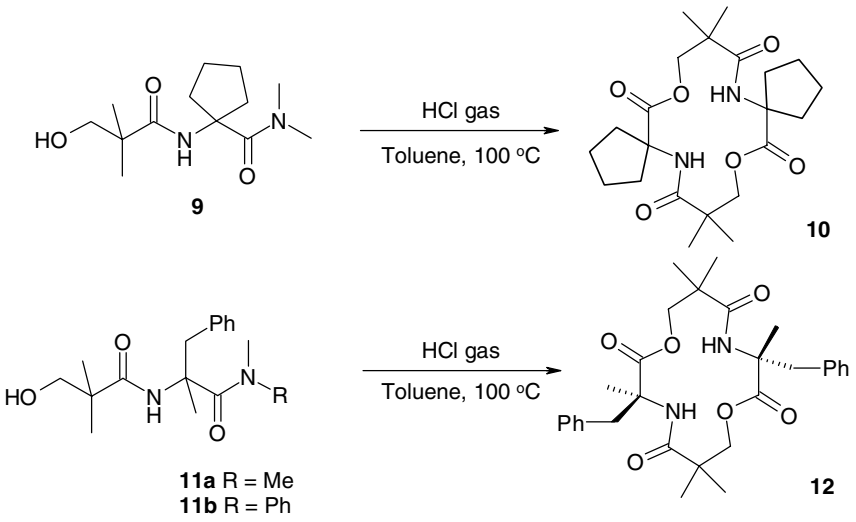
The reason for the preferred dimerization in the case of **1** is most probably a defined conformation of the linear precursor and the stability of the transition state. Another reason could be the rigidity of the amide bond in **1**, although the reactions with an ester analogue of compound **1** showed that again oligomerization occurred to give tri- and tetrameric structures of the β-hydroxy acid.[1] Therefore, most probably the dimerization is not a result of the amide bond rigidity.

In order to further investigate the cyclodimerization of dipeptide analogues of type **1** under the conditions of the 'direct amide cyclization' we synthesized some other amide precursors, which differ in the substitution in the α-amino acid as well as in the β-hydroxy acid moiety, including chiral compounds. Furthermore, we tried to get some information from computer modeling of key compounds.

2. Results and discussion

It is known from previous experiments[5-7,19,20] that dipeptides of type **1**, in which the two methyl groups in the amino acid residue are replaced by a cyclopentane ring (*i.e.* the compounds contain 1-aminocyclopentane carboxylic acid instead of 1-aminoisobutyric acid (Aib)), react in a very similar way to **1**. Therefore, our first target was amide **9**, which was conveniently prepared by the coupling of 3-hydroxy-2,2-dimethylpropanoic acid with *N*,*N*-dimethyl-1-azaspiro[2.4]hept-1-en-2-amine in analogy to Ref. 1 ('azirine/oxazolone method'; see also Ref. 21). After bubbling HCl gas through a solution of **9** in toluene (20 mM) at 100 °C for 4 min, 88% of the corresponding 14-membered cyclodepsipeptide **10** was obtained (Scheme 3). Similarly, the linear racemic dipeptides **11a,b**[22] carrying two different substituents on the C(α) atom, were also synthesized by

the 'azirine/oxazolone method'. 'Direct amide cyclization' of **11b** yielded, upon cyclization, 68% of the dimeric racemic **12** as the sole product.

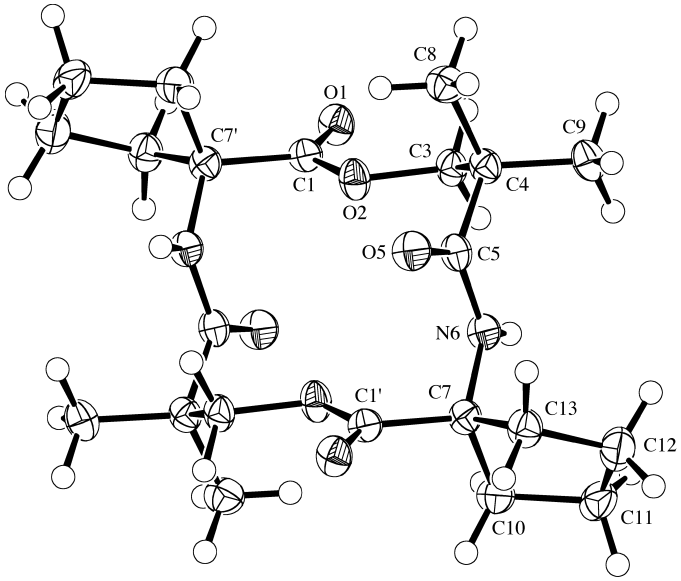


Scheme 3

This was clearly indicated by the ^{1}H and ^{13}C spectra, which show only one set of signals. The structures of **10** and **12** were established by X-ray crystallography (Figure 1).

The backbones of the two structures are very similar and also resemble the structures of the previously reported tetramethyl analogue **3**.[1] In the case of **10,** the molecule sits about a crystallographic centre of inversion. The cyclopentane ring has an envelope conformation with the spiro C-atom as the envelope flap. Each amide NH group forms an intermolecular hydrogen bond with a lactone carbonyl O-atom of an adjacent molecule. The molecular symmetry results in there being two parallel hydrogen bonds running in opposite directions between each molecule. These interactions link the molecules into extended double-bridged chains which run parallel to the [1 0 0] direction. Taken individually, the repeat unit in the chain generated by one of the interactions has a graph set motif[24] of C(5). The pair of hydrogen bonds linking two adjacent molecules forms a loop with a graph set motif of $R_2^2(16)$.

a)



b)

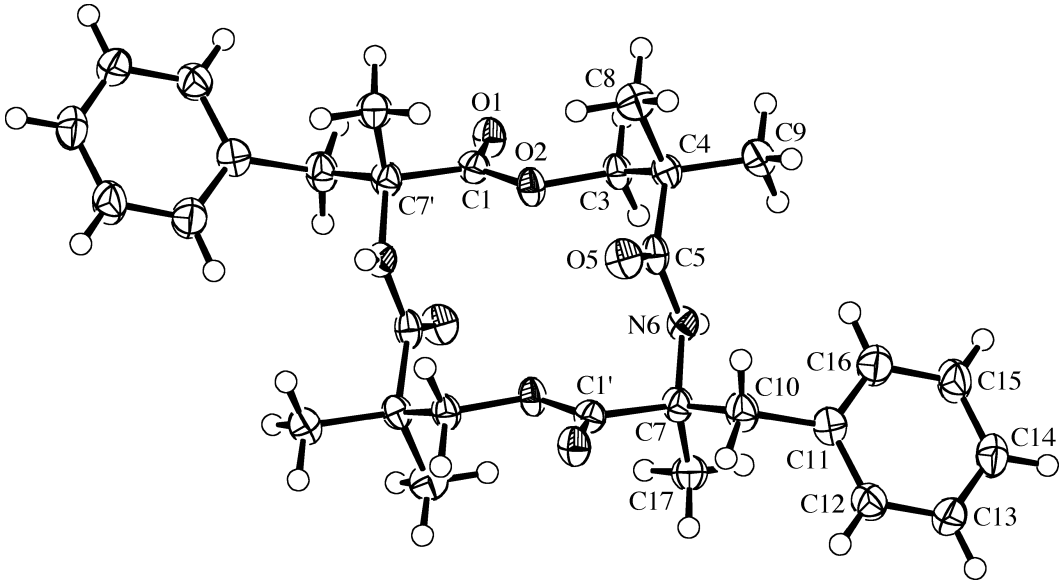


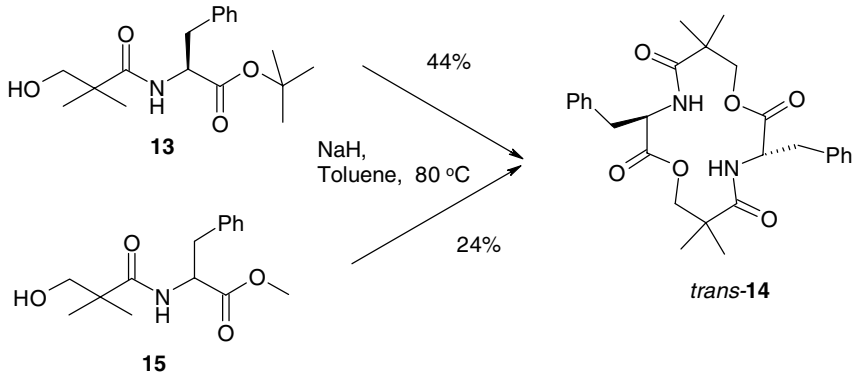
Figure 1. *ORTEP plots*[23] of the molecular structures of a) **10** and b) **12** (50% probability ellipsoids, arbitrary numbering of atoms).

In the case of **12,** the space group is centrosymmetric and therefore the crystals are racemic. The molecule again sits about a crystallographic centre of inversion, so therefore has the (7*RS*, 7'*SR*)-

configuration, *i.e.* **12** is the *trans*-isomer. The hydrogen bonding pattern in the crystals of **12** is the same as for **10.**

The nature of the cyclodimerization in the case of **11** is remarkable. Starting with a racemic precursor **11,** one would expect that a mixture of *cis*- and *trans*-substituted cyclodimers would be obtained, but only the *trans*-isomer **12** has been formed in 68% yield.

As mentioned before, factors that might influence the cyclization are not only the type, but also the number of substituents in the amino acid moiety. Therefore, a cyclization experiment was carried out with an analogue of **11,** which contains a monosubstituted amino acid. Direct amide cyclization was not an option in this case, since the intermediate oxazolone does not form smoothly in the case of monosubstituted substrates[25]. Therefore, we used the base catalyzed lactonization described in Ref. 10. The coupling of 3-hydroxy-2,2-dimethylpropanoic acid with L-Phe-O*t*Bu.HCl gave the enantiomerically pure **13**. When a solution of **13** was heated in toluene (200 mM) in the presence of 1 equiv of NaH, the 14-membered cyclic depsipeptide *trans*-**14** was obtained as the only isolable product in 44% yield. In order to compare the configurations of the two stereogenic centers, the analogous cyclization was performed with a racemic starting material, *i.e.* methyl ester **15** (Scheme 4). Surprisingly, a single cyclodepsipeptide was again obtained in 24% yield and was identical with *trans*-**14** in all respects.

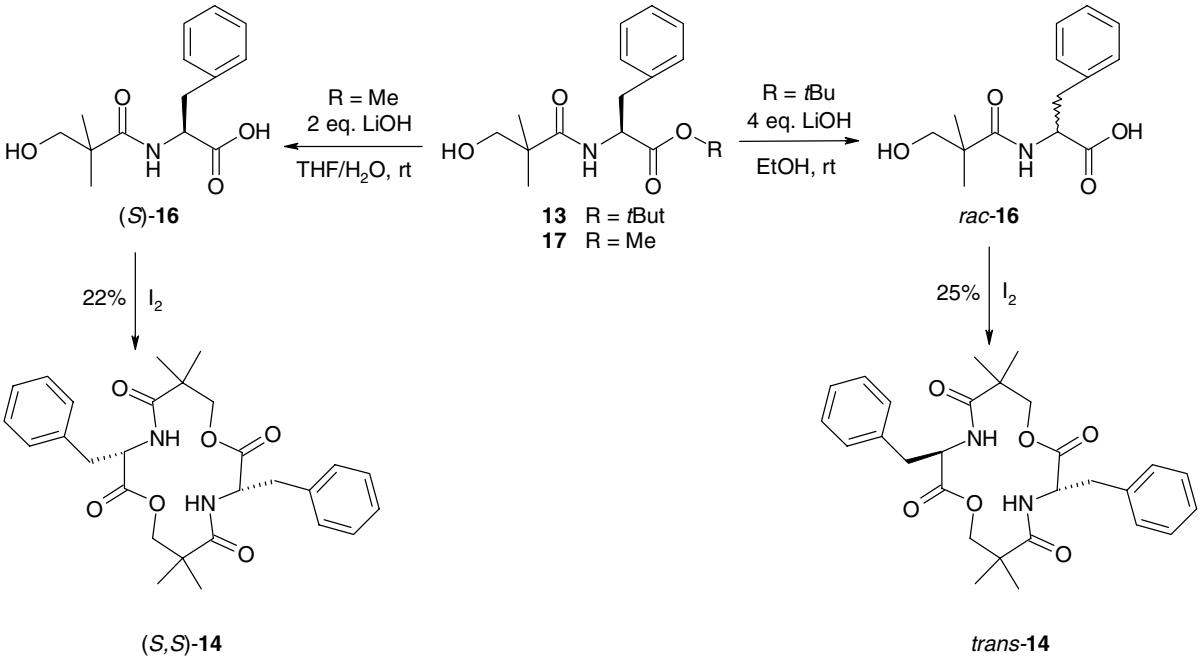


Scheme 4

The ^{1}H NMR spectrum of the cyclized product obtained from **13** using a shift reagent (*Pirkle* reagent) and HPLC on a chiral adsorbent (*Chiracel* OD-H, *Merck* Whelk-O 1) showed the

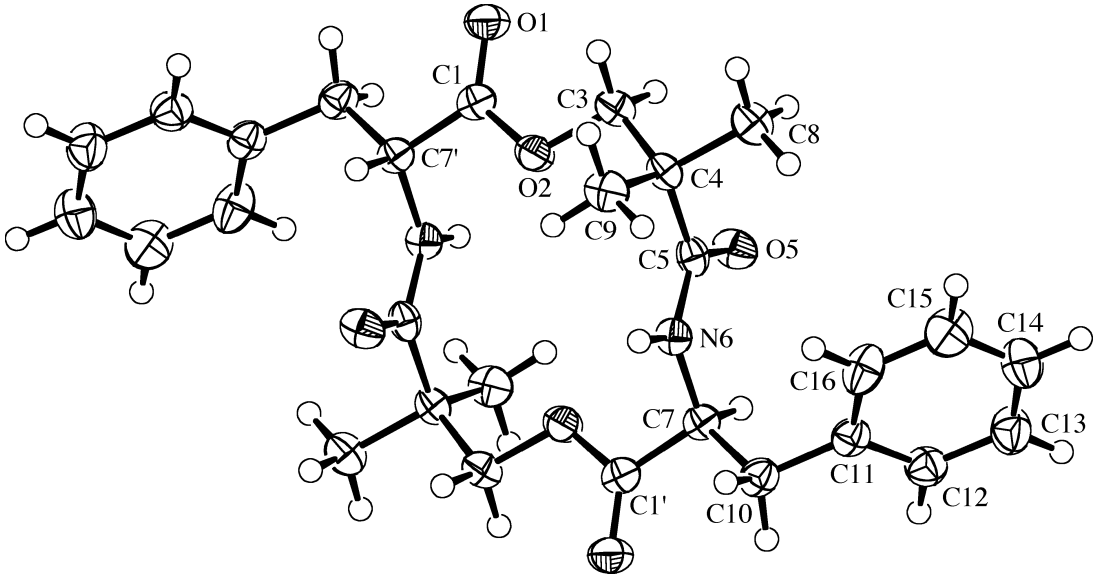
presence of only one compound, which was identical with the product obtained from the cyclization of **15**. X-ray crystallography of both products confirmed their identical structure and proved that the benzyl groups are *trans*-oriented (Figure 2).

As the precursor **13** was optically active ($[\alpha]_D^{25}$= +44.6, c = 1, $CHCl_3$), an inversion of the configuration at one of the stereogenic centers has taken place during the cyclization step. With the aim of avoiding this inversion, another cyclization was attempted with the corresponding free hydroxy acid **16**, which was obtained from the basic hydrolysis of **13**. Cyclization of both *rac*-**16** and *(S)*-**16** was achieved under neutral conditions using I_2 as a catalyst,[26] which has previously proven to be efficient for the synthesis of depsipeptide **3**.[1] The product obtained from *rac*-**16** was again the racemic *trans*-**14a,** while the enantiomerically pure acid (*S*)-**16,** obtained by a milder hydrolysis of its methyl ester **17**, yielded also only one cyclodepsipeptide, namely *(S,S)*-**14** (Scheme 5).



Scheme 5

a)



b)

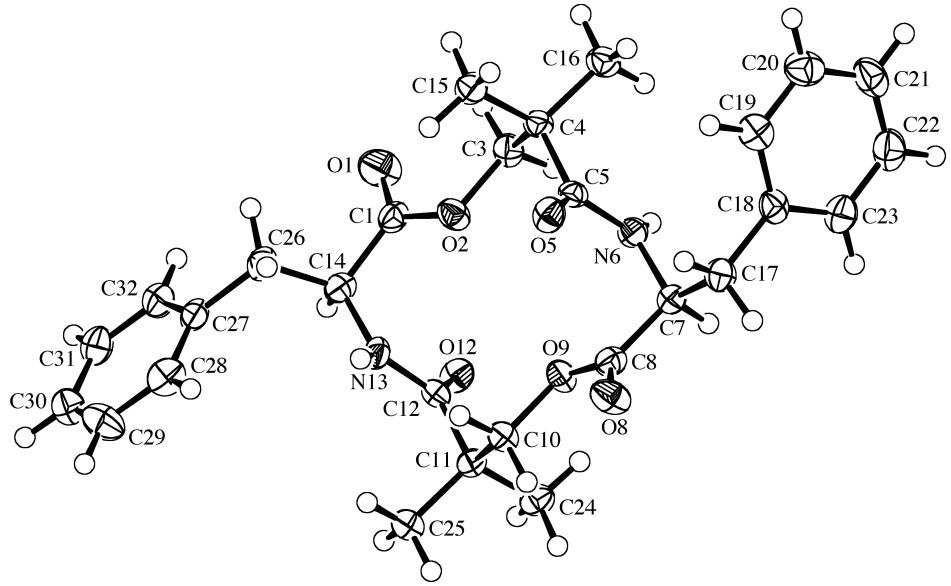


Figure 2. *ORTEP plots*[23] of the molecular structures of a) *trans*-**14** and b) molecule A of *(S,S)*-**14** (50% probability ellipsoids, arbitrary numbering of atoms).

Since the space group of *trans*-**14** is centrosymmetric, the crystals are racemic. The molecule sits about a crystallographic centre of inversion, so the two stereogenic centres have inverted

configurations, *i.e.* (7*RS*, 7'*SR*). The hydrogen bonding pattern is again analogous to that of **12** and **10**.

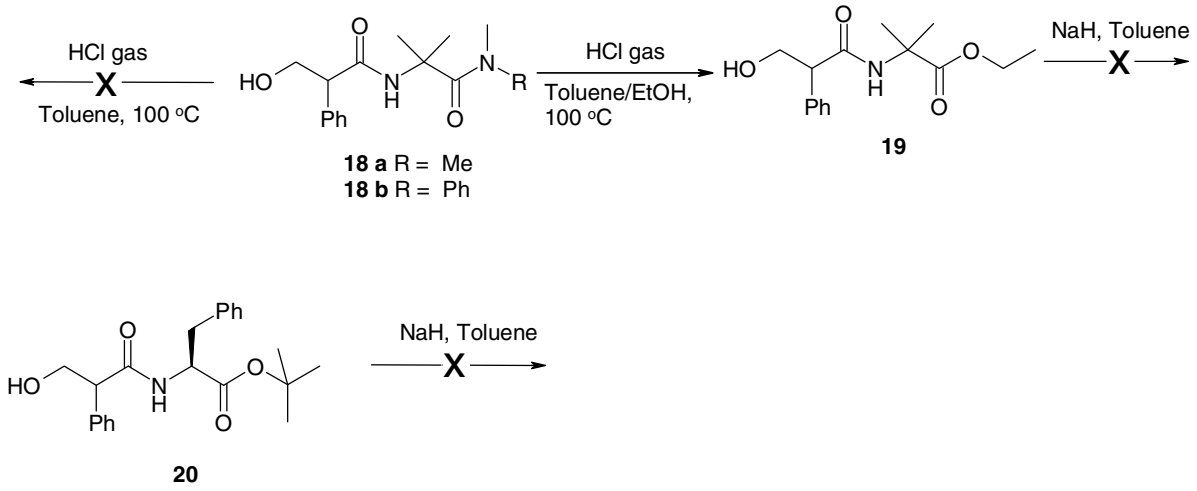
Analytical HPLC of both of these compounds on a chiral column (Whelk-O 1 column, hexane/EtOH 10:1) clearly shows two different peaks with retention times of 10.8 and 10.9 min, respectively. The HPLC diagram of a mixture of the two compounds under the same conditions also showed two peaks, proving once more their different structure. Furthermore, it was shown, that *(S,S)*-**14** is optically active. For this reason, we expected that it is the *cis*-isomer with the (*S,S*)-configuration, which was subsequently proven by X-ray crystallography (Figure 2).

In the crystal structure of *(S,S)*-**14,** there are two symmetry-independent molecules in the asymmetric unit, but the conformations of the two molecules are almost identical. The space group permits the compound in the crystal to be enantiomerically pure, but the absolute configuration of the molecule has not been determined. The enantiomer used in the refinement was based on the expected (*S*)-configuration of each chiral centre in the molecule. The crystal is merohedrally twinned, with twin operator [1 0 0 / 0 -1 0 / 0 0 -1] and the major twin domain has a volume fraction of 0.640(1). Each amide group in molecule A forms an intermolecular hydrogen bond with an amide O-atom of an adjacent molecule A. This results in there being two parallel hydrogen bonds running in opposite directions between each molecule. The interactions link the molecules into extended double-bridged ···A···A···A··· chains which run parallel to the [1 0 0] direction. Taken individually, the repeat unit in the chain generated by one of the interactions has a graph set motif[24] of C(4). The pair of hydrogen bonds linking two adjacent molecules forms a loop with a graph set motif of $R_2^2(18)$. The molecules of type B are similarly linked into extended double-bridged ···B···B···B··· chains which also run parallel to the [1 0 0] direction.

From these results it could be concluded that monosubstituted amino acid blocks in amides of type **1** do not prevent the cyclodimerization. Next, the influence of the disubstitution of C(α) of the β-hydroxy acid should be investigated and, therefore, analogous dipeptides with a α-monosubstituted β-hydroxy acid were synthesized and subjected to cyclization procedures. Being readily available, tropic acid (3-hydroxy-2-phenylpropanoic acid) turned out to be an interesting

starting material for this study. Thus, amides **18a** and **18b** were prepared by coupling tropic acid with 2,2,*N*,*N*-tetramethyl-2*H*-azirin-3-amine and 2,2,*N*-trimethyl-*N*-phenyl-2*H*-azirin-3-amine, respectively, and subjected to the conditions of the 'direct amide cyclization'. Surprisingly, the cyclization failed and only traces of the corresponding 1,3-oxazol-5(4*H*)-one were identified in the crude reaction mixture by IR and NMR spectroscopy. Column chromatography led to no identifiable products. Furthermore, the corresponding ethyl ester **19**, derived from either of the amides **18** by treatment with HCl gas in EtOH, did not yield cyclic products upon treatment with NaH. Other lactonization procedures, proven to be successful in the case of amide derivatives,[1] also failed to give the desired cyclic depsipeptide in this case (Scheme 6).

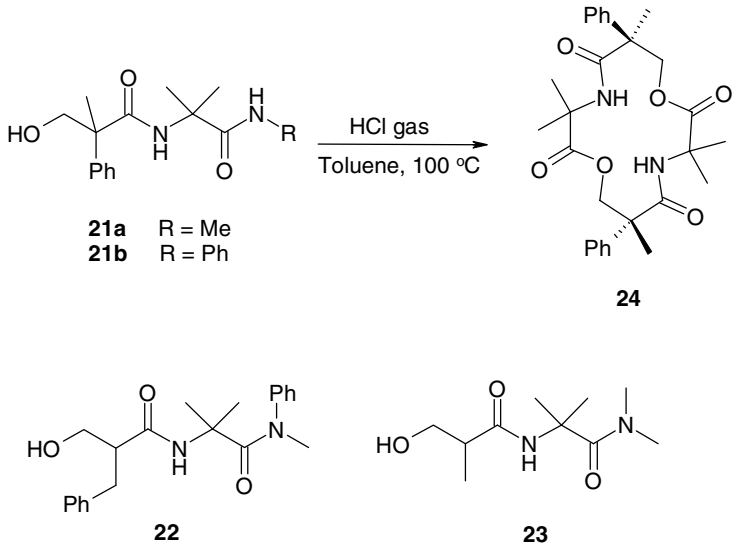
When tropic acid was coupled with L-phenylalanine *t*-butylester.HCl, amide **20** was obtained as a mixture of two diastereoisomers. Their separation on a Whelk-O 1 preparative HPLC column proved to be possible, and we attempted to cyclize them separately, in order to determine the stereospecificity of the NaH cyclization. Unfortunately both the racemic and the enantiomerically pure substrates failed to give cyclic depsipeptides (Scheme 6).



Scheme 6

The reason for the failure of cyclization of **18-20** could be a steric hindrance of the phenyl group in the α-position or its electronic effect. To examine this possibility, 3-hydroxy-2-methyl-2-phenylpropanoic acid was prepared[27] and coupled with the corresponding 2*H*-azirin-3-amines to

give **21a,b**. The third explanation could be that the cyclization is thermodynamically unfavorable when the substrate is monosubstituted in the α-position of the β-hydroxy acid moiety. Therefore, α-benzyl-β-hydroxypropanoic acid and β-hydroxyisobutyric acid were synthesized according to known procedures[28] and coupled with 2,2,*N*,*N*-tetramethyl-2*H*-azirin-3-amine to give amides **22** and **23,** respectively, as substrates for the cyclization (Scheme 7).



Scheme 7

As expected, amide **21b** cyclized under DAC conditions to yield the 14-membered cyclodepsipeptide **24** in moderate yield. This result suggests that amides of type **18**/**21** bearing a phenyl group at C(α) of the hydroxy acids do cyclize when α,α-disubstituted, *i.e*. the phenyl group in **18** was not the reason for its failure to give cyclic products. Compound **24** was isolated as a colorless solid, which showed only one set of signals in the NMR spectra. Therefore it could be suggested that only one stereoisomer, as a racemate, has been obtained. Careful crystallization from a mixture of toluene/acetonitrile/acetone gave crystals suitable for X-ray crystallography. The molecular structure of **24** is depicted in Figure 3, showing that again the *trans*-isomer has been obtained.

Since the space group is centrosymmetric, the compound is racemic. The molecule sits about a crystallographic centre of inversion, so therefore has the (4*RS*,4'*SR*)-configuration. Remarkably,

the amide groups are not involved in any hydrogen bonds. Although amide O-atoms in adjacent molecules appear to be positioned correctly to accept a hydrogen bond from the amide H-atom, the H···O distance of 2.98 Å is much too long for it to be considered a hydrogen bond. This is probably the result of molecular bulk preventing the molecules packing close enough together for intermolecular hydrogen bonds to form.

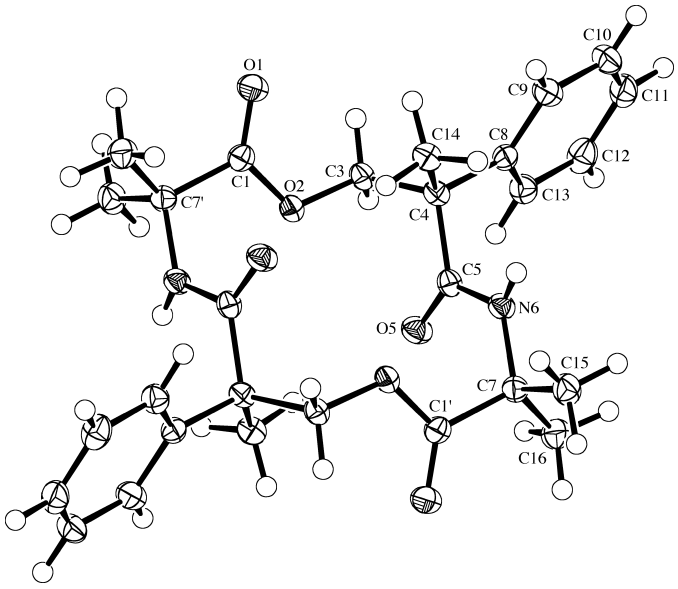
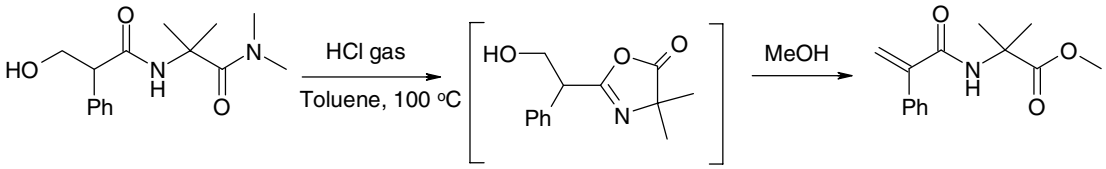


Figure 3. *ORTEP plot*[23] of the molecular structure of **24** (50% probability ellipsoids, arbitrary numbering of atoms).

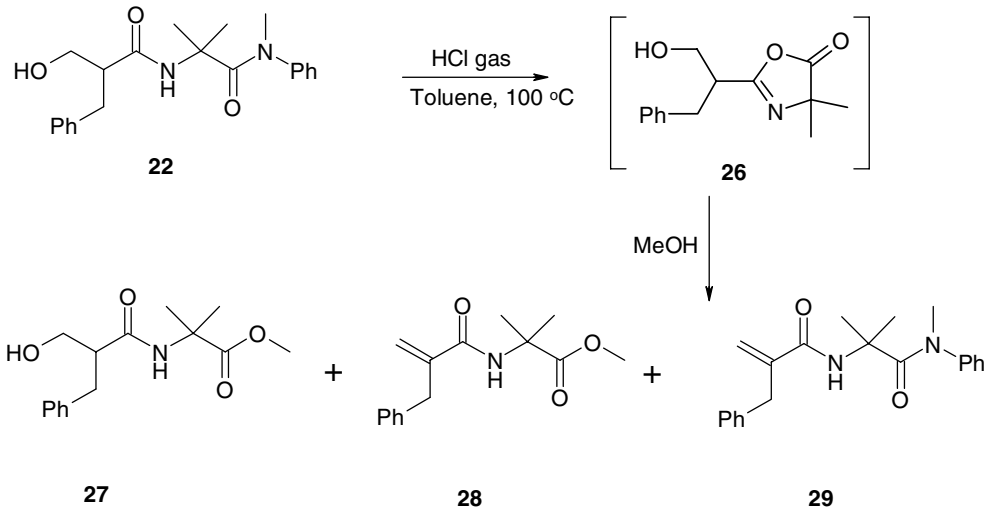
Amides **22** and **23** failed to cyclize under the DAC reaction conditions, as was the case with **18**. Upon monitoring the reaction of **18** by IR spectroscopy, the formation of the corresponding 1,3-oxazol-5(4*H*)-one **25**, which is the expected intermediate in the cyclization reaction, was observed (strong absorption at 1820-1830 cm^{-1}),[29] and after addition of methanol to the reaction mixture, methyl ester **26** was isolated in 58% yield (Scheme 8).



18 **25** **26**

Scheme 8

The formation of a methyl ester and the IR spectra strongly suggest the presence of a 1,3-oxazol-5(4*H*)-one as an intermediate. It seems that the oxazolone formation and water elimination in the case of **18** are competitive reactions. In order to get an indication of which reaction takes place first, a similar set of experiments was carried out with benzyl derivative **22**. Upon bubbling HCl gas through a solution of **22** in toluene/methanol (20%), the only product obtained was the corresponding hydroxy ester **27** (Scheme 9). When the reaction was carried out under the conditions described for **18**, *i.e.* oxazolone formation with HCl gas in toluene (monitoring by IR, increasing absorption at 1826 cm^{-1}) and addition of methanol after saturation, the dehydrated ester **28** and the dehydrated amide **29** were obtained in addition to **27** (Scheme 9).



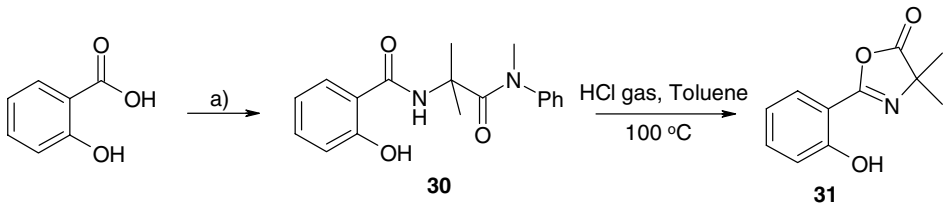
22 **26** **27** **28** **29**

Scheme 9

This result suggests that when the reaction is carried out in the presence of a nucleophile, such as methanol, oxazolone **26** is formed first and is immediately transformed into the corresponding

hydroxy ester **27**. On the other hand, in the absence of a nucleophile, the intermediate oxazolone **26** eliminates water, leading to 2-vinyl oxazolones and thus preventing further cyclization. The formation of **28** and **29** can be explained by the competitive ring opening of **26** by the nucleophiles methanol and *N*-methylaniline, respectively. This result is an additional indication that the cyclodimerization process occurs *via* an oxazolone intermediate.

Another variation of the starting materials for the direct amide cyclization (DAC) is the insertion of aromatic β-hydroxy acids or β-hydroxycycloalkane carboxylic acids. The first of these derivatives, salicylamide **30**, was obtained from salicylic acid by coupling with the corresponding 2*H*-azirin-3-amine (Scheme 10).[5,19]



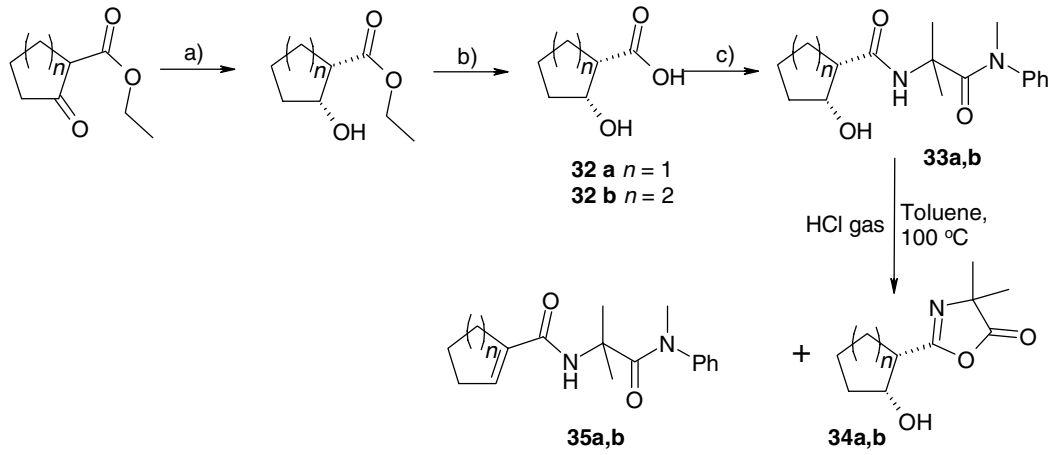
a) 2,2,*N*-Trimethyl-*N*-phenyl-2*H*-azirin-3-amine,THF

Scheme 10

Compound **30** was subjected to the DAC conditions. The starting material disappeared quickly (TLC), but even after 35 min the only product formed was the corresponding oxazolone **31**. After its isolation, further exposure to the same reaction conditions did not propagate the reaction further, and the oxazolone **31** was recovered. The stability of the oxazolone is in this case extremely high, and apparently a ring enlargement reaction is sterically disfavored.

Crystals of **31** suitable for X-ray crystal structure determination were grown from a mixture of deuterochloroform and dichloromethane by slow evaporation of the solvent. The five membered heterocycle is planar and the phenyl residue is almost coplanar with the ring. The hydroxy group forms an intramolecular hydrogen bond with the imine N-atom. The interaction can be described by the graph set motif[24] of S(6) (for crystallographic details see exper. part).

Next, the aromatic ring in **30** was replaced by a cycloaliphatic one. The preparation of the precursors **33a,b** was achieved in three steps according to Scheme 11. The cyclization under the standard conditions led to a mixture of two products, the oxazolone **34** and the dehydrated amide **35,** but no cyclodepsipeptide could be detected.

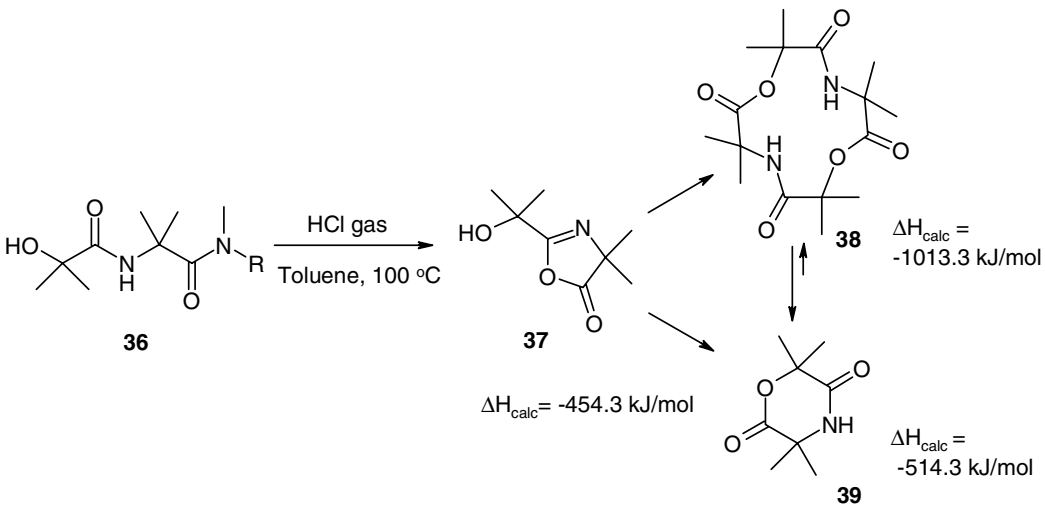


a) Yeast, H_2O; Ref. 32; b) LiOH, THF/H_2O; c) 2,2,*N*-Trimethyl-*N*-phenyl-2*H*-azirin-3-amine,THF.

Scheme 11

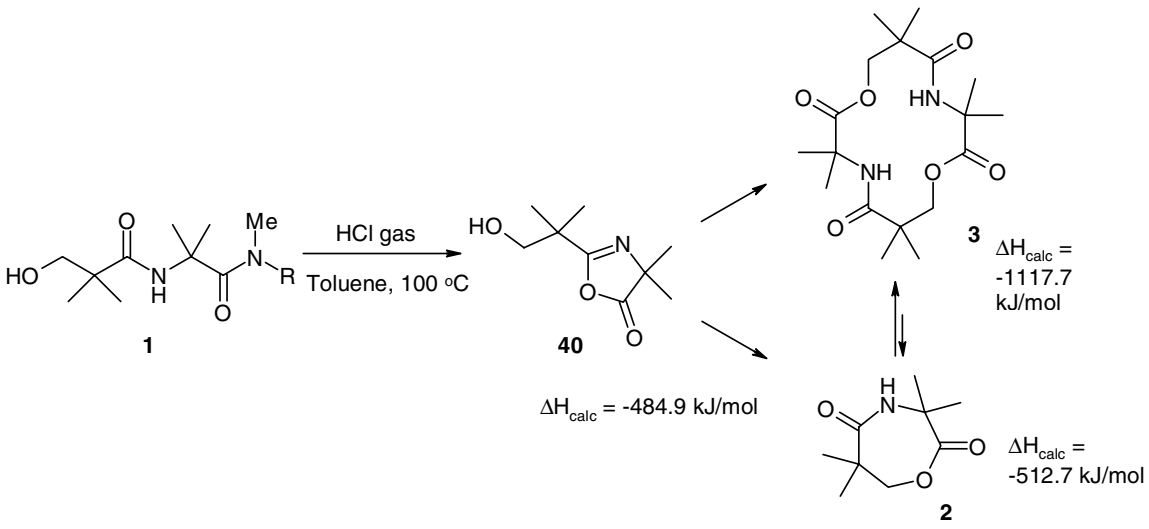
3. Computer Modeling

As we were searching for an explanation for the preferred cyclodimerization process of diamides of type **1**, we carried out some simple quantum mechanical calculations. Especially surprising was the discrepancy with the lower homologue **36**, which under the DAC conditions gave the cyclic monomer **39** exclusively. Assuming that the reaction proceeds indeed *via* the oxazolone intermediates (**37** and **40,** respectively), we compared the energies of the corresponding monomeric and dimeric ring structures, both in the cases of α-hydroxy acids and β-hydroxy acids (Schemes 12 and 13).



Scheme 12

AM1 calculations[30] with *Ampac* v.6.5.5[31] revealed that the transition state required to achieve a nucleophilic attack of the oxazolone hydroxy group on the carbonyl C-atom is more favorable in the case of **40** than in **37**, which is to be expected, having in mind the length of the alkyl chain to which the OH group is bound. Nevertheless, under the DAC conditions, **36** gives **39**, whereas **1** undergoes the twinning process.



Scheme 13

Direct comparison of the heats of formation (ΔH) of **38** and **39,** as well as those of **3** and **2,** reveals that in the first case (Scheme 12) the formation of the dimer **38** is energetically more unfavorable than the formation of the monomer **39** ($2E_{39} < E_{38}$). In the second case (Scheme 13), formation of the dimer **3** is energetically more favorable than the formation of the monomer ($2E_2 > E_3$), which suggests that the cause for the different products formed is thermodynamic. This crude modeling helps to understand why the dimers of type **3** could be the main products of the direct amide cyclization of **1**, but it does not explain why they are the only products formed. An equilibrium between the monomeric and dimeric forms under the strongly acidic conditions of the DAC is to be expected in both cases (between **2** and **3** on the one hand and between **39** and **38** on the other). This equilibrium might be shifted almost completely in one direction in the case of **3** and in the other in the case of **39**.

4. Conclusions

Upon investigating the reasons for the cyclodimerization of β-hydroxy acid amides of type **1** under various conditions, we were able to isolate five different 14-membered cyclodimers of type **3.** Although other coupling methods also gave moderate results, the best yields were obtained *via* the 'direct amide cyclization' (DAC), reaching 88% for the cyclodimer **10**. It is worth mentioning that in all cases, when starting with racemic material, only the *trans*-substituted cyclodepsipeptides were isolated.

The cyclodimerization is most probably a result of the greater thermodynamic stability of the 14-membered ring compared with the 7-membered one. Another factor which might contribute to the cyclodimerization, as suggested in the literature, is H-bond formation, which would be more pronounced in the 14-membered ring, although the structures of all cyclodepsipeptides which were characterized by X-ray crystallography showed no evidence of intramolecular H-bonding.

Molecular modeling using simple AM1 calculations shows in the case of **1** that the formation of the dimeric depsipeptide is indeed thermodynamically favored over the formation of the monomer, but it does not explain why the 14-membered ring is the only product formed. A mixture of the monomeric and dimeric forms is to be expected. Thus, the reason for the exclusive

cyclodimerization of compounds of type **1** remains unclear and further investigation in this area is needed.

Variation in the substitution pattern of the starting compounds showed that mono-substitution in the amino acid moiety does not prevent twinning (**13**, **15** and **16** yielded *trans*-**14,** although not *via* DAC). Using I_2 mediated lactonization allowed for the selective synthesis of both *(S,S)*-**14** (starting with (*S*)-**16**) and *trans*-**14** (starting with *rac*-**16**). If, on the other hand, the hydroxy acid moiety is monosubstituted (as in **18, 19, 27**), although the formation of the intermediate 1,3-oxazol-5(*4H*)-one has been monitored by IR, water elimination occurs and no cyclic products are formed. Therefore, the synthesis of β-hydroxy acid containing cyclic depsipeptides *via* DAC is useful only if the starting amides contain α,α-disubstituted acids.

5. Experimental Part

5.1. General.

Thin-layer chromatography (TLC): Merck TLC aluminium sheets, silica gel 60 F_{254}. Prep. TLC: Merck PLC plates (glass), silica gel 60 F_{254}, 2 mm and 40-63 μm. Flash chromatography (CC): Uetikon-Chemie 'Chromatographiegel' C-560. Mp: Büchi 540 apparatus, uncorrected. IR Spectra: Perkin-Elmer Spectrum one spectrometer; in KBr, unless otherwise stated, absorption bands in cm^{-1}. ^1H NMR (300 MHz) and ^{13}C NMR (75.5 MHz) spectra: Bruker ARX-300 or Bruker DRX-600 instrument; ^1H NMR (600 MHz) and ^{13}C NMR (150 MHz); in $CDCl_3$ at 300 K; TMS as internal standard, unless otherwise stated; δ in ppm, coupling constants *J* in Hz. Mass spectrometry (MS): Finnigan MAT-90 for electron impact ionization (EI), Finnigan SSQ-700 for chemical ionization (CI, with NH_3) and electrospray ionization (ESI, in MeOH + NaI), unless otherwise stated.

2,2,*N*,*N*-Tetramethyl-2*H*-azirin-3-amine, 2,2,*N*-trimethyl-*N*-phenyl-2*H*-azirin-3-amine, 2-benzyl-2,*N*-dimethyl-*N*-phenyl-2*H*-azirin-3-amine and *N*,*N*-dimethyl-1-azaspiro[2.4]hept-1-en-2-amine were prepared according to standard procedures (Refs. 5 and 7 and refs. cited therein). 3-Hydroxy-2-benzylpropanoic acid was prepared by the method of *Monteil et al.*[28] and methyltropic acid from hydroptropic aldehyde by hydroxymethylation, followed by oxidation, according to

Geffken.[27] Hydroxy acids **32** were synthesized by the method of *Seebach et al*.[32] All other products used were commercially available.

General procedure 1 (GP1).

To a solution of a hydroxy acid (2-6 mmol) in dry THF (5-20 mL), 1.05 equiv of the corresponding 2*H*-azirin-3-amine were added dropwise. The mixture was stirred at rt for 12-36 h, the solvent evaporated and the remaining solid purified by column chromatography (CC) over silica gel and dried in h.v.

General procedure 2 (GP2).

According to GP1, the reaction was stirred overnight, the solvent evaporated, the solid residue washed with Et_2O and recrystallized from AcOEt.

General procedure 3 (GP3).

To a solution of a hydroxy acid (3 mmol) in dry THF (10 mL) was added the corresponding phenylalanine ester hydrochloride (3.0 mmol) and 3-(diethoxyphosphoryloxy)-1,2,3-benzotriazine-4(3*H*)-one (DEPBT, 916 mg, 98%, 3.0 mmol). To the cooled mixture were added dropwise 12 mmol (1.21 g) Et_3N. The mixture was stirred at rt overnight, the solvent was partially evaporated, AcOEt was added and the solution was washed with 5% aq $KHSO_4$ and with saturated aq $NaHCO_3$ solutions. The combined organic fractions were dried over $MgSO_4$, evaporated, purified by CC, and dried in h.v.

General Procedure 4 (GP4).

To a solution of an ester (2.0 mmol) in 10 mL EtOH was added $LiOH.H_2O$ (336 mg, 8 mmol). The reaction was stirred overnight at rt, acidified with 6N HCl, the organic solvent was evaporated *in vacuo* and the residue extracted with AcOEt. The crude acids were used in the next reaction step without further purification.

General procedure 5 (GP5).

A suspension of an amide (1 mmol) in dry toluene (50 mL) was heated to 100 ^oC, and dry HCl gas was bubbled through the suspension for 5-15 min. Then, the mixture was allowed to cool to rt

while bubbling N_2 through it (*ca*. 20 min). The solvent was evaporated, the white residue was washed with 3×15 mL of CH_2Cl_2 and dried in h.v.

General procedure 6 (GP6).

According to GP5, after bubbling N_2 through the reaction mixture (*ca*. 20 min) the solvent was evaporated, and the residue purified by CC.

General procedure 7 (GP7).

To a solution of **13** or **15** (1 mmol) in dry toluene (5 mL), NaH (40 mg of a 60% suspension in mineral oil, 1 mmol) was added slowly at 0 ^oC and under constant stirring (N_2-atmosphere). After 6 h at 80 ^oC, the mixture was acidified with 0.1N HCl (~5 mL) to pH 5 and extracted with CH_2Cl_2 The combined organic fractions were dried ($MgSO_4$) and evaporated i.v. The crystalline residue was purified by CC (CH_2Cl_2/acetone 200:1) and dried in h.v.

General procedure 8 (GP8).

To a solution of a hydroxy acid (1 mmol) in acetonitrile (5 mL), I_2 (25 mg, 0.1 mmol) was added. After 2 d under reflux, the mixture was cooled and the solvent evaporated. After addition of 20 mL of AcOEt and washing with aq $Na_2S_2O_3$, the combined organic fractions were dried ($MgSO_4$) and evaporated i.v. The crystalline residue was purified by CC.

General Procedure 9 (GP9).

A suspension of an amide (1 mmol) in a toluene/20% ethanol solution (60 mL) was heated to 100 ^oC, and dry HCl gas was bubbled through the suspension for 10 min. Then, the mixture was allowed to cool to rt while bubbling N_2 through it (*ca*. 20 min). The solvent was evaporated and the oily residue was purified by CC .

General Procedure 10 (GP10).

A suspension of an amide (0.5 mmol) in dry toluene (25 mL) was heated to 100 ^oC, and dry HCl gas was bubbled through the suspension for 10 min. Then, the mixture was allowed to cool to rt while bubbling N_2 through it (*ca*. 20 min). The solvent was removed i.v. and MeOH (15 mL) was

added to the residue and stirred at rt for 1 h in the presence of 500 mg SiO_2. The silicagel was filtered, the solvent was evaporated and the oily residue was purified by CC.

5.2. Preparation of 3-hydroxy-2-methylpropanoic acid. To a solution of methyl (*R*)-3-hydroxy-2-methylpropanoate (1.0 g, 8.38 mmol) in THF/water 75:10 (10 mL) LiOH (1.55g, 33.5 mmol) was added at 0 °C. The mixture was stirred overnight, the organic solvent evaporated, the residue acidified with 6N HCl to pH 1 and extracted with AcOEt. The colorless oil was used in the next reaction without further purification. Yield: 768 mg (88%). Spectroscopic data in accordance with previously published data.[33] The optical purity has not been determined. ^{1}H NMR((D$_6$)-DMSO): 1.04 (d, *J* = 5.9 Hz, CH_3); 2.31-2.38 (m, CH); 3.38-3.44, 3.52-3.61 (2m, CH_2); 4.62 (br s, OH); 11.95 (br s COOH).

5.3. Coupling of β-hydroxy acids with 2*H*-azirin-3-amines

5.3.1. 3-Hydroxy-2,2-dimethyl-*N*-[1-(*N*,*N*-dimethylcarbamoyl)cyclopentyl]propanamide (**9**). According to GP1, 3-hydroxy-2,2-dimethylpropanoic acid (806 mg, 6.84 mmol) in dry THF (10 mL), *N*,*N*-dimethyl-1-azaspiro[2.4]hept-1-en-2-amine (1.037 g, 7.52 mmol), 18 h, CC (SiO_2, acetone/CH_2Cl_2 1:20). Yield: 1.330 g (76%) of **9**. White solid. Mp 180.6-181.9 °C (AcOEt). IR: 3397vs, 3279s, 2960s, 2873m, 1644vs, 1542vs, 1469m, 1393s, 1309m, 1257m, 1212w, 1164m, 1119w, 1061s, 1011w, 983w, 911w, 817w, 669m. ^{1}H NMR ((D$_6$)-DMSO): 1.14 (s, Me_2C); 1.71 (m, $2CH_2$); 1.81-2.00, 2.28-2.48 (2m, $2CH_2$); 2.99 (s, Me_2N); 3.56 (br s, OH); 4.46 (s, CH_2O); 7.42 (br s, NH). ^{13}C NMR ((D$_6$)-DMSO): 22.8 (q, *Me*$_2$C); 24.2 (t, CH_2); 37.2 (t, CH_2); 37.7 (q, Me_2N); 42.8, 66.2 (2s, 2C); 69.1 (t, CH_2O); 172.7, 176.9 (2s, 2CO). CI-MS: 257 (21, $[M+H]^+$), 212.3 (100, $[M\text{-}NMe_2]^+$). Anal. calcd for $C_{13}H_{24}N_2O_3$ (256.35): C 60.91, H 9.44, N 10.93; found: C 60.24, H 9.50, N 10.76.

5.3.2. 3-Hydroxy-2,2-dimethyl-*N*-[1-methyl-1-(*N*,*N*-dimethylcarbamoyl)-2-phenylethyl]-propanamide (11a). According to GP1, 3-hydroxy-2,2-dimethylpropanoic acid (436 mg, 2.00 mmol) in dry THF (5 mL), 2-benzyl-2,*N*,*N*-trimethyl-2*H*-azirin-3-amine (395 mg, 2.1 mmol), 24 h, CC (SiO_2, acetone/CH_2Cl_2 1:20). Yield: 538 mg (88%) of **11a**. White powder. Mp 92.6-94.9 °C. ^{1}H NMR ((D$_6$)DMSO): 1.05 (s, Me_2C); 1.29 (s, Me); 3.09 (s, Me_2N); 3.13-3.38 (m, PhCH_2);

3.54 (s, CH_2O); 4.77 (br s, OH); 6.92 (br s, NH); 7.06-7.36 (m, Ph). ^{13}C NMR ((D_6)DMSO): 22.4 (q, *Me*$_2$C); 24.8 (q, Me); 37.3 (q, MeN); 41.0 (s, Me$_2$*C*); 43.8 (t, Ph*C*H$_2$); 70.1 (t, CH_2O); 128.3, 128.8, 129.4 (3d, 5 arom. CH); 136.1 (s, arom. C); 173.1, 175.2 (2s, 2 CO). CI-MS: 307 (100, $[M+H]^+$), 262 (25, $[M-NMe_2]^+$).

Recrystallization from DMSO/diethyl ether yielded crystals of **11a**, suitable for an X-ray crystal structure determination.

5.3.3. 3-Hydroxy-2,2-dimethyl-*N*-[1-methyl-1-(*N*-methyl-*N*-phenylcarbamoyl)-2-phenylethyl]propanamide (11b). According to GP1, 3-hydroxy-2,2-dimethylpropanoic acid (436 mg, 2.00 mmol) in dry THF (5 mL), 2-benzyl-2,*N*-dimethyl-*N*-phenyl-2*H*-azirin-3-amine (525 mg, 2.1 mmol), 28 h, CC (SiO_2, acetone/CH_2Cl_2 1:30). Yield: 618 mg (84%) of **11b**. White powder. Mp 62.0-64.2 °C. IR: 3385vs, 3291vs, 3060m, 2941vs, 1701vs, 1634vs, 1591s, 1454s, 1386s, 1312s, 1238s, 1193m, 1165m, 1111m, 1053s, 886m, 908w, 834w, 772s, 705s. ^{1}H NMR: 0.98, 1.08 (2s, Me$_2$C); 1.33 (s, Me); 3.29 (s, MeN); 3.41 (m, PhC*H*$_2$); 3.54 (s, CH_2O); 3.77 (br s, OH); 6.89 (br s, NH); 7.12-4.10 (m, 2Ph). ^{13}C NMR: 22.1 (q, *Me*$_2$C); 24.1 (q, Me); 41.8 (q, MeN); 43.4 (s, Me$_2$*C*); 43.7 (t, Ph*C*H$_2$); 70.4 (t, CH_2O); 127.1, 128.3, 128.8, 129.5, 130.1 (5d, 10 arom. CH); 136.1, 144.2 (2s, 2arom. C); 173.0, 177.1 (2s, 2 CO). CI-MS: 369 (30, $[M+H]^+$), 262 (100, $[M-N(Me)Ph]^+$), 234.2 (20), 160.1 (18), 134.1(36), 107.1 (26). Anal. calcd for $C_{22}H_{28}N_2O_3$ (368.48): C 71.71, H 7.66, N 7.60; found: C 71.79, H 7.82, N 7.07.

5.3.4. 3-Hydroxy-2-phenyl-*N*-[1-methyl-1-(*N*,*N*-dimethylcarbamoyl)ethyl]propanamide (18a). According to GP2, 3-hydroxy-2-phenylpropanoic acid (tropic acid, 332 mg, 2.00 mmol) in dry THF (5 mL), 2,2,*N*,*N*-tetramethyl-2*H*-azirin-3-amine (249 mg, 2.1 mmol), 8 h. Yield: 440 mg (79%) of **18a**. White powder. Mp 160.8-161.3 °C (AcOEt). IR: 3421m, 3296s, 3060m, 2936m, 1651vs, 1619vs, 1540s, 1491m, 1454w, 1396s, 1271m, 1219m, 1123s, 1068m, 1051m, 913w, 750m, 702m. ^{1}H NMR: 1.88, 1.94 (2s, Me$_2$C); 3.28 (s, Me$_2$N); 3.87-4.12 (m, CH_2); 4.42 (br t, J = 6.8Hz, CH); 6.98 (s, NH); 7.50-7.62 (m, Ph). ^{13}C NMR: 24.3, 24. 5 (2q, *Me*$_2$C); 38.0 (q, Me$_2$N); 56.9 (s, Me$_2$*C*); 54.7 (d, CH); 64.9 (t, CH_2O); 127.7, 128.2, 129.0 (3d, 5 arom. CH); 136.7 (s, arom. C); 171.9, 172.6 (2s, 2CO). ^{1}H NMR ((D_6)DMSO): 1.38, 1.32 (2s, Me$_2$C); 2.71 (s, Me$_2$N); 3.42-3.58, 3.60-3.69, 3.87-3.94 (3m, CH, CH_2); 4.78 (t, OH); 7.22-7.36 (m, Ph); 8.31 (s, NH). ^{13}C NMR ((D_6)DMSO): 25.5, 25.8 (2q, *Me*$_2$C); 37.0 (q, Me$_2$N); 53.9 (s, Me$_2$*C*); 55.4 (d, CH); 63.2 (t,

CH_2O); 126.6, 127.7, 128.0 (3d, 5 arom. CH); 138.1 (s, arom. C); 170.2, 171.7 (2s, 2CO). CI-MS: 279 (80, $[M+H]^+$), 234 (100, $[M-NMe_2]^+$), 206 (22), 157 (18), 104 (8).

5.3.5. 3-Hydroxy-2-phenyl-*N*-[1-methyl-1-(*N*-methyl-N-phenylcarbamoyl)ethyl]-propanamide (18b). According to GP2, 3-hydroxy-2-phenylpropanoic acid (tropic acid, 332 mg, 2.00 mmol) in dry THF (5 mL), 2,2,*N*-trimethyl-*N*-phenyl-2*H*-azirin-3-amine (365 mg, 2.1 mmol), 9 h. Yield: 578 mg (85%) of **18b**. White powder. Mp 128.6-129.9 °C (AcOEt). IR: 3298s, 3274s, 3055m, 2940m, 1673vs, 16124vs, 1545s, 1488m, 1462w, 1394s, 1270m, 1124s, 1099s, 1060m, 913m, 745m. ^{1}H NMR: 1.76, 1.89 (2s, Me_2C); 3.31 (s, MeN); 3.91-4.19 (m, CH_2); 4.36-4.42 (m, CH); 7.05 (s, NH); 7.41-7.55, 7.60-7.87 (2m, 2Ph). ^{13}C NMR: 24.6, 24. 8 (2q, *Me*$_2$C); 41.1 (*q*, MeN); 57.4 (s, Me$_2$*C*); 55.0 (d, CH); 67.3 (t, CH_2O); 127.6, 127.7, 128.2, 128.5, 128.8, 129.1 (6d, 10 arom. CH); 136.7, 143.8 (2s, 2arom. C); 173.1, 173.9 (2s, 2CO). ESI-MS: 363 (100, $[M+Na]^+$).

5.3.6. 3-Hydroxy-2-methyl-2-phenyl-*N*-[1-methyl-(*N*,*N*-dimethylcarbamoyl)ethyl]-propanamide (**21a**). According to GP1, 3-hydroxy-2-methyl-2-phenylpropanoic acid (360 mg, 2.00 mmol) in dry THF (5 mL), 2,2,*N*,*N*-tetramethyl-2*H*-azirin-3-amine (249 mg, 2.1 mmol), 36 h, CC (SiO_2, acetone/CH_2Cl_2 1:10). Yield: 455 mg (78%) of **21a**. Colorless crystals. Mp 147.6-148.4 °C (toluene). IR: 3533s, 3280vs, 3054s, 2928vs, 1708vs, 1622vs, 1526vs, 1394s, 1264s, 1208s, 1118s, 1050m, 976m, 900w, 770m, 751m, 802m. ^{1}H NMR: 1.50 (s, Me_2C); 1.61 (s, Me), 3.00 (*s*, Me_2N); 3.55-3.70, 4.05-4.19 (2m, CH_2O); 4.45 (br s, OH); 7.18-7.41 (m, Ph, NH). ^{13}C-NMR: 21.4 (q, *Me*$_2$C); 25.0 (q, Me); 37.7 (q, Me_2N); 51.5, 56.4 (2s, 2Me$_2$*C*); 68.7 (t, CH_2O); 126.5, 126.9, 128.3 (3d, 5 arom. CH); 141.5 (s, arom. C); 172.6, 175.3 (2s, 2CO). CI-MS: 293 (88, $[M+H]^+$), 248 (100, $[M-NMe_2]^+$), 113 (28). Anal. calcd for $C_{16}H_{24}N_2O_3$ (292.38): C 65.73, H 8.27, N 9.58; found: C 65.69, H 8.40, N 9.59.

5.3.7. 3-Hydroxy-2-methyl-2-phenyl-*N*-[1-methyl-1-(*N*-methyl-*N*-phenylcarbamoyl)-ethyl]propanamide (21b). According to GP1, 3-hydroxy-2-methyl-2-phenylpropanoic acid (360 mg, 2.00 mmol) in dry THF (5 mL) 2-benzyl-2,*N*-dimethyl-*N*-phenyl-2*H*-azirin-3-amine (365 mg, 2.1 mmol), 28 h, CC (SiO_2, acetone/CH_2Cl_2 1:20). Yield: 608 mg (86%) of **21b**. White solid. Mp 132.1-133.0 °C. IR: 3451s, 3282vs, 3057m, 2992s, 1709s, 1635vs, 1592s, 1445s,

1395s, 1262m, 1157m, 1123m, 1092s, 1026s, 921m. ^{1}H NMR: 1.30, 1.38 (2s, Me_2C); 1.48 (s, Me), 3.22 (s, MeN); 3.55-3.61, 4.00-4.10 (2m, CH_2O); 4.63 (br s, OH); 6.61 (br *s*, NH); 7.18-7.41 (m, 2Ph). ^{13}C NMR: 21.8 (q, *Me*$_2$C); 25.7 (q, Me); 41.5 (q, MeN); 52.3, 58.8 (2s, 2Me$_2$*C*); 69.2 (t, CH_2O); 126.3, 126.6, 126.9, 127.1, 127.2, 128.1, 128.3, 128.4, 128.6, 129.4 (10d, 10 arom. CH); 141.6, 144.2 (2s, 2arom. C); 173.7, 176.0 (2s, 2CO). ESI-MS: 731 (48, $[2M+Na]^+$), 377 (100, $[M+Na]^+$), 248 (16).

5.3.8. 3-Hydroxy-2-benzyl-*N*-[1-methyl-1-(*N*-methyl-*N*-phenylcarbamoyl)ethyl]-propanamide (**22**). According to GP2, 3-hydroxy-2-benzylpropanoic acid (360 mg, 2.00 mmol) in dry THF (5 mL), 2,2,*N*-trimethyl-N-phenyl-2*H*-azirin-3-amine (365 mg, 2.1 mmol), 8 h. Yield: 560 mg (79%) of **22**. White powder. Mp 162.4-163.9 ^{o}C. IR: 3409m, 3277s, 3060w, 2932m, 1630vs, 1592s, 1544s, 1493s, 1395s, 1254m, 1188w, 1092s, 1070m, 769m, 743m, 703s, 617m. ^{1}H NMR: 1.27, 1.33 (2s, Me_2C); 2.38-2.42, 2.61-2.73, 2.88-3.01 (3m, CH_2, CH); 3.27 (s, MeN); 3.66-3.73 (m, OH); 6.18 (br s, NH); 7.11-7.41 (m, 2Ph). ^{13}C NMR: 26.2, 27. 0 (2q, *Me*$_2$C); 34.3 (t, CH_2); 41.5 (q, MeN); 50.8 (d, CH); 59.0 (*s*, Me$_2$*C*); 63.6 (t, CH_2O); 126.3, 128.2, 128.3, 128.5, 129.0, 129.4 (6d, 10 arom. CH); 139.3, 144.4 (2s, 2arom. C); 173.8, 174.0 (2s, 2CO). ESI-MS: 377 (100, $[M+Na]^+$). Anal. calcd for $C_{16}H_{24}N_2O_3$ (354.45): C 65.73, H 8.27, N 9.58; found: C 60.24, H 9.50, N 10.76.

5.3.9. 3-Hydroxy-2-methyl-*N*-[1-methyl-1-(*N*,*N*-dimethylcarbamoyl)ethyl]propanamide (23). According to GP1, 3-hydroxy-2-methylpropanoic acid (416 mg, 4.00 mmol) in dry THF (5 mL), 2,2,*N*,*N*-tetramethyl-2*H*-azirin-3-amine (498 mg, 4.2 mmol), 38 h, CC (SiO_2, acetone/CH_2Cl_2 1:20). Yield: 790mg (83%) of **23**. Colorless crystals. Mp 118.7-120.0 ^{o}C. IR: 3418s, 1619vs, 1540s, 1397s, 1279m, 1226s, 1124s, 1077m, 1036m. ^{1}H NMR: 1.09 (d, J = 6.1 Hz, Me); 1.58 (s, Me_2C); 2.59 (m, CH); 3.06 (s, Me_2N); 3.63 (d, CH_2); 4.21 (br s, OH); 7.70 (s, NH). ^{13}C NMR: 13.7 (q, Me); 25.5, 25. 6 (2q, *Me*$_2$C); 37.9 (q, MeN); 56.3 (*s*, Me$_2$*C*); 42.3 (d, CH); 64.8 (t, CH_2O); 173.0, 174.9 (2s, 2CO). ESI-MS: 455 (20, $[2M+Na]^+$), 239 (100, $[M+Na]^+$). Anal. calcd for $C_{10}H_{20}N_2O_3$ (216.28): C 55.53, H 9.32, N 12.95; found: C 55.74, H 9.71, N 13.12.

5.3.10. 2-Hydroxy-*N*-[1-methyl-1-(*N*-methyl-*N*-phenylcarbamoyl)ethyl]benzamide (30). According to GP1, salicylic acid (276 mg, 2.00 mmol) in dry THF (5 mL), 2,2,*N*-trimethyl-*N*-

phenyl-2*H*-azirin-3-amine (365 mg, 2.1 mmol), CC (SiO_2, acetone/CH_2Cl_2 1:20). Yield: 565mg (92%) of **30**. Colorless crystals. Mp 146.1-147.8 °C . IR: 3533s, 3280vs, 3054s, 2928vs, 1708vs, 1622vs, 1526vs, 1394s, 1264s, 1208s, 1118s, 1050m, 976m, 900w, 770m, 751m, 802m. ^{1}H NMR: 1.43 (s, Me_2C); 3.22 (s, MeN); 6.68-6.74 (m, 1arom. H); 6.76 (br s, NH); 6.92-7.0 (m, 2H arom);7.11-7.28 (m, 4arom. H); 7.31-7.42 (m, 2arom. H); 12.1 (s, OH). ^{13}C NMR: 26.4 (q, *Me*$_2$C); 41.4 (q, MeN); 58.4 (s, Me$_2$*C*); 119.9 (s, arom. C); 126.6, 126.8, 127.3, 127.9, 128.2, 128.9, 129.3 (7d, 9 arom. CH); 134.1, 142.2 (2s, 2arom. C); 172.9, 177.5 (2s, 2CO). ESI-MS: 335 (100, [*M*+Na]$^+$).

5.3.11. (1*R*,2*S*)-2-Hydroxy-*N*-[1-methyl-1-(*N*-methyl-*N*-phenylcarbamoyl)ethyl]-cyclopentanecarbonamide (33a) According to GP1, (1*R*,2*S*)-2-hydroxycyclopentanoic acid (**32a,** 260 mg, 2.00 mmol) in dry THF (5 mL), 2,2,*N*-trimethyl-*N*-phenyl-2*H*-azirin-3-amine (365 mg, 2.1 mmol), CC (SiO_2, acetone/CH_2Cl_2 1:10). Yield: 530 mg (86%) of **33a**. White powder. Mp 153.4-155.0 °C. IR: 3289s, 2943s, 1708vs, 1636vs, 1593s, 1494s, 1390s, 1240s, 1092s, 1028m, 919m, 732s. ^{1}H NMR: 1.42 (s, Me_2C); 1.57-1.68, 1.70-1.77, 1.79-1.96 (3m, 3CH_2, CH); 3.27 (s, MeN); 4.35 (m, CHO); 6.38 (br s, NH); 7.24-7.41 (m, Ph, NH). ^{13}C NMR: 21.9 (t, CH_2); 26.1, 26.4 (2q, *Me*$_2$C); 26.8, 33.9 (2t, 2CH_2); 41.4 (q, MeN); 50.2 (d, CH); 58.6 (s, Me$_2$*C*); 74.2 (d, CHO); 128.1, 128.3, 129.4 (3d, 5 arom. CH); 144.2 (s, arom. C); 173.4, 176.1 (2s, 2CO). ESI-MS: 327 (100, [*M*+Na]$^+$).

5.3.12. (1*R*,2*S*)-2-Hydroxy-*N*-[1-methyl-1-(*N*-methyl-*N*-phenylcarbamoyl)ethyl]-cyclohexanecarbonamide (33b). According to GP1, (1*R*,2*S*)-2-hydroxycyclohexanoic acid (**32b**, 288 mg, 2.00 mmol) in dry THF (5 mL), 2,2,*N*-trimethyl-*N*-phenyl-2*H*-azirin-3-amine (365 mg, 2.1 mmol), 12 h, CC (SiO_2, acetone/CH_2Cl_2 1:10).Yield: 566 mg (89%) of **33b**.White powder. Mp 171.2-172.9 °C. IR: 3290s, 3020m, 2948s, 1711vs, 1635vs, 1599s, 1491s, 1421m, 1391s, 1239s, 1091s, 1022m, 919m, 731s. ^{1}H NMR: 1.37, 1.42 (2s, Me_2C); 1.43-1.52, 1.62-1.74, 1.77-1.83, 1.86-1.95 (4m, 4CH_2, CH); 3.21 (s, MeN); 3.97 (m, CHO); 6.41 (br s, NH); 7.22-7.41 (m, Ph, NH). ^{13}C NMR: 19.2, 24.4, 24.9 (3t, 3CH_2); 25.9, 26.1 (2q, *Me*$_2$C); 31.7 (t, CH_2); 41.4 (q, MeN); 47.9 (d, CH); 59.4 (s, Me$_2$*C*); 66.7 (d, CHO); 127.9, 128.2, 129.3 (3d, 5 arom. CH); 142.2 (s, arom. C); 172.1, 177.4 (2s, 2CO). ESI-MS: 341 (100, [*M*+Na]$^+$).

5.4. Preparation of dipeptide esters

5.4.1. *tert*-Butyl (*S*)-2-(3-hydroxy-2,2-dimethylpropanoylamino)-3-phenylpropanoate (13). According to GP3, 3-hydroxy-2,2-dimethylpropanoic acid (654 mg, 3 mmol), L-phenylalanine *tert*-butyl ester hydrochloride (774 mg, 3.0 mmol), CC (SiO_2, acetone/CH_2Cl_2 1:30). Yield: 857 g (89%) of **13.** Colorless solid. Mp 82.7-84.1 °C. $[\alpha]_D^{25}$ = +44.6 (c = 1, $CHCl_3$). IR: 3265vs, 3006s, 2982vs, 2867s, 1721vs, 1635vs, 1543vs, 1455s, 1392s, 1315s, 1165vs, 1102m, 963s, 850m. ^{1}H NMR: 1.09 (s, Me_2C); 1.45 (s, Me_3C), 3.00-3.17 (m, PhCH_2); 3.42-3.51 (m, CH_2O); 3.72 (br s, OH); 4.63-4.78 (m, CH); 6.94 (br s, NH); 7.13-7.36 (m, Ph). ^{13}C NMR: 22.3 (q, Me_2C); 27.8 (q, Me_3C); 37.6 (t, CH_2); 43.1 (s, Me_2C); 53. (d, CH); 69.9 (t, CH_2); 82.3 (s, Me_3C); 126.9, 128.3, 129.3 (3d, 5 arom. CH); 136.1 (s, arom. C); 170.8, 177.1 (2s, 2CO). CI-MS: 322 (88, $[M+H]^+$), 266 (100, $[M-\ ^t\text{Bu}]^+$). Anal. calc. for $C_{18}H_{27}NO_4$ (321.42): C 67.26, H 8.47, N 4.36; found: C 67.04, H 8.66, N 4.20.

5.4.2. Methyl (*RS*)-2-(3-hydroxy-2,2-dimethylpropanoylamino)-3-phenylpropanoate (15). According to GP3, 3-hydroxy-2,2-dimethylpropanoic acid (654 mg, 3 mmol), DL-phenylalanine methyl ester hydrochloride (639 mg, 3.0 mmol), CC (SiO_2, acetone/CH_2Cl_2 1:30). Yield: 673 g (80%) of **15.** Pale yellow oil. ^{1}H NMR: 1.03 (s, Me_2C); 2.98-3.12 (m, PhCH_2); 3.36-3.49 (m, CH_2O); 3.67 (s, MeO); 4.68-74 (m, CH); 6.50 (br s, NH); 7.13-7.38 (m, Ph). ^{13}C NMR: 22.2 (q, Me_2C); 37.6 (t, CH_2); 43.0 (s, Me_2C); 52.2 (d, CH); 52.9 (q, MeO); 69.5 (t, CH_2); 127.0, 128.4, 129.1 (3d, 5 arom. CH); 135.8 (s, arom. C); 172.2, 177.3 (2s, 2CO). CI-MS: 280 (100, $[M+H]^+$), 162 (18). Anal. calcd for $C_{15}H_{13}NO_4$ (279.34): C 64.50, H 7.58, N 5.01; found: C 64.15, H 7.73, N 4.89.

5.4.3. Methyl (*S*)-2-(3-hydroxy-2,2-dimethylpropanoylamino)-3-phenylpropanoate (17). According to GP3, 3-hydroxy-2,2-dimethylpropanoic acid (654 mg, 3 mmol), L-phenylalanine methyl ester hydrochloride (639mg, 3.0 mmol), CC (SiO_2, acetone/CH_2Cl_2 1:30). Yield: 720 g (86%) of **17.** Pale yellow oil. ^{1}H NMR: 1.05 (s, Me_2C); 3.00-3.09 (m, PhCH_2); 3.38-3.48 (m, CH_2O); 3.69 (s, MeO); 4.71 (t, J = 6.0 Hz, CH); 6.52 (s, NH); 7.14-7.36 (m, Ph). ^{13}C NMR: 22.3 (q, Me_2C); 37.7 (t, CH_2); 43.0 (s, Me_2C); 52.1 (d, CH); 53.0 (q, MeO); 69.6 (t, CH_2); 127.0,

128.4, 129.1 (3d, 5 arom. CH); 135.9 (s, arom. C); 172.3, 177.5 (2s, 2CO). CI-MS: 280 (100, $[M+H]^+$), 162 (18).

5.4.4. *tert*-Butyl (*R,S*)-2-(3-Hydroxy-2-phenylpropanoylamino)-3-phenylpropanoate (20). According to GP3, tropic acid (498 mg, 3 mmol), L-phenylalanine *tert*-butyl ester hydrochloride (774 mg, 3.0 mmol), CC (SiO_2, acetone/CH_2Cl_2 1:30). Yield: 974 mg (88%) of **20**. Pale yellow crystals. Mp 117.4-119.1 °C. IR: 3426s, 3290s, 3059m, 1738vs, 1658vs, 1635s, 1551m, 1454m, 1368s, 1223s, 1154vs, 1059m, 1023m, 845m, 740m, 701s. ^{1}H NMR ((D$_6$)DMSO): 1.28, 1.31 (2s, Me_3C); 2.91-3.10 (m, $PhCH_2$); 3.50-3.62, 3.69-3.80 (2m, CH_2O); 4.00-4.16, 4.60-4.78 (2m, 2CH); 5.81-6.00 (m, OH); 6.73 (d, J = 3.7 Hz, NH); 6.93-7.27 (m, 2Ph). ^{13}C NMR: 27.8, 27.9 (2q, *Me*$_3$C); 37.7 (t, CH_2); 53.1, 53.5, 54.3, 54.4 (4d, 2CH); 64.7, 64.8 (t, CH_2O); 81.8 (s, Me_3C); 127.7, 128.2, 128.3, 128.4, 129.0, 129.3 (6d, 10 arom. CH); 136.1, 136.8 (2*s*, 2arom. C); 171.0, 173.2 (2s, 2 CO). CI-MS: 370 (85, $[M+H]^+$), 313(100, $[M - {}^t\text{Bu})]^+$).

5.5. Saponification of dipeptide amides

5.5.1. *(RS)*-2-(3-Hydroxy-2,2-dimethylpropanoylamino)-3-phenylpropanoic acid (*rac*-16). According to GP4, from **13** (642 mg, 2.0 mmol). Yield 454 mg (79%) of **13**. White solid. Mp 91.3-94.9 °C. ^{1}H NMR: 0.99, 1.02 (2s, Me_2C); 2.96-3.02, 3.08-3.14 (2m, $PhCH_2$); 3.21-3.41 (m, CH_2O); 4.66-4.78 (m, CH); 6.95 (br s, NH); 6.98-7.18 (m, Ph). ^{13}C NMR: 22.0 (q, *Me*$_2$C); 37.0 (t, CH_2); 43.3 (s, Me_2C); 53.1 (d, CH); 69.3 (t, CH_2); 127.0, 128.4, 129.3 (3d, 5 arom. CH); 135.8 (s, arom. C); 174.0, 178.1 (2s, 2CO). ESI-MS: 288 (100, $[M+H]^+$).

5.5.2. (*S*)-2-(3-Hydroxy-2,2-dimethylpropanoylamino)-3-phenylpropanoic acid ((*S*)-16). According to GP4, from **17** (558 mg, 2.0 mmol). Yield: 442 mg (79%) of **(*S*)-16**. Colorless oil, $[\alpha]_D^{25}$ = +44.1 (c = 1, $CHCl_3$). IR: 3369vs, 3192s, 2963s, 1723vs, 1643vs, 1529vs, 1455s, 1394m, 1287m, 1254s, 1179m, 1111w, 1049s, 913w, 699s. ^{1}H NMR: 0.99, 1.01 (2s, Me_2C); 2.88-2.94, 3.02-3.14 (2m, $PhCH_2$); 3.38 (m, CH_2O); 4.71-4.83 (m, CH); 6.71 (br s, NH); 6.98-7.18 (m, Ph). ^{13}C NMR: 21.1 (q, *Me*$_2$C); 36.1 (t, CH_2); 42.4 (s, Me_2C); 52.2 (d, CH); 68.5 (t, CH_2); 126.1,

127.6, 128.4 (3d, 5 arom. CH); 134.9 (s, arom. C); 173.2, 177.2 (2s, 2CO). ESI-MS: 288 (100, $[M+Na]^+$).

5.6.Solvolysis of dipeptide amides under DAC conditions

5.6.1. Ethyl 2-(3-hydroxy-2-phenylpropanoylamino)-2-methylpropanoate (19). According to GP9, **18** (278 mg, 1 mmol) in toluene/EtOH 80/20 (60 mL), CC (AcOEt/hexane 1:10). Yield: 209 mg (76%) of **19**. Colorless oil. IR: 3237vs, 3068s, 2980s, 1734vs, 1642vs, 1557s, 1475s, 1383m, 1288s, 1164s, 1070m, 1037s, 872w, 751m, 699s. ^{1}H NMR: 1.10 (t, J = 6.1 Hz, Me); 1.42 (s, Me_2C); 3.50-3.60, 3.63-3.72 (2m, CH_2); 3.91-4.13 (m, CH, CH_2); 6.02 (s, OH); 7.11-7.29 (m, Ph, NH). ^{13}C NMR: 13.9 (q, Me); 24. 5 (q, Me_2C); 54.4 (d, CH); 56.6 (s, Me_2C); 61.5 (t, CH_2); 65.1 (t, CH_2O); 127.7, 128.3, 129.0 (3d, 5 arom. CH); 136.5 (s, arom. C); 172.8, 174.2 (2s, 2CO). ESI-MS: 280 (100, $[M+H]^+$).

5.6.2. Methyl 2-methyl-2-(2-phenylacryloylamino)propanoate (26). According to GP10, **18** (139 mg, 0.5 mmol) in toluene (30 mL), CC (AcOEt/hexane 1:10). Yield: 72 mg (58%) of **26.** White crystals. Mp 116.8-117.4 ^{o}C. IR: 3328m, 3068m, 2960vs, 2861s, 1727vs, 1657s, 1533s, 1460s, 1382m, 1276vs, 1139s, 1073s, 944w, 731m. ^{1}H NMR: 1.56 (s, Me_2C); 3.77 (s, MeO); 5.60, 6.10 (2*s*, H_2C=); 6.28 (br s, NH); 7.30-7.42 (m, Ph). ^{13}C NMR: 24.6 (q, Me_2C); 52.6 (s, MeO); 56.7 (s, Me_2C); 121.7 (t, H_2C=); 127.9, 128.6, 128.9 (3d, 5 arom. CH); 136.8 (s, C=CH_2); 144.7 (s, arom. C); 166.6, 174.7 (2s, 2CO). CI-MS: 265(6, $[M+NH_4]^+$), 249 (14), 248 (100, $[M+H]^+$).

5.6.3. Methyl 2-(2-benzyl-3-hydroxypropanoylamino)-2-methylpropanoate (27). According to GP9, **22** (188 mg, 0.5 mmol) in toluene/MeOH 80/20 (30 mL), CC (AcOEt/hexane 1:10). Yield: 81 mg (58%) of **22.** Colorless oil. ^{1}H NMR: 1.41, 1.44 (2s, Me_2C); 2.59 (m, CH); 2.82 (m, CH_2); 3.51, (br s, OH); 3.71 (m, MeO, CH_2); 6.50 (s, NH); 7.11-7.31 (m, Ph). ^{13}C NMR: 26.3 (q, Me_2C); 35.2 (t, CH_2); 48.4 (s, MeO); 51.1 (d, CH); 55.1 (s, Me_2C); 66.0 (t, CH_2); 126.6, 128.4, 128.9 (3d, 5 arom. CH); 138.0 (s, arom. C); 170.9, 172.9 (2s, 2CO). CI-MS: 281 (16), 280 (100, $[M+H]^+$).

5.7.Attempted cyclization reactions

5.7.1. Direct Amide Cyclisation

5.7.1.1. 8,8,19,19-Tetramethyl-10,21-dioxa-6,17-diazadispiro[4.6.4.6]docosane-7,11,18,22-tetraone (10). According to GP5, **9** (256 mg, 1 mmol) in dry toluene (50 mL) for 15 min. Yield: 186 mg (88%) of **10**. White powder. Mp 344.8-346.4 °C (decomp). IR: 3386vs, 3029w, 2989s, 2936s, 1715vs, 1668vs, 1519vs, 1470m, 1268vs, 1190m, 1126vs, 1012m, 804w, 699s. ^{1}H NMR ((D$_7$)DMF): 1.00 (s, 2Me$_2$C); 1.46-1.54 (m, 4CH$_2$); 1.75-1.82, 1.88-1.94 (2m, 4CH$_2$); 3.94 (s, 2CH$_2$O); 7.69 (s, 2NH). ^{13}C NMR ((D$_7$)DMF): 22.8 (q, 2*Me*$_2$C); 24.7, 36.1 (2t, 8CH$_2$); 41.3, 65.2 (2s, Me$_2$*C*, 2C); 70.8 (t, 2CH$_2$O); 173.9 174.5 (2s, 4CO). CI-MS: 441 (21), 440 (90, [*M*+Na]$^+$), 423 (100, [*M*+H]$^+$). Anal. calcd for $C_{22}H_{34}N_2O_6$ (422.53): C 62.54, H 8.11, N 6.63; found: C 61.89, H 8.07, N 6.56.

Recrystallization from DMF/toluene/ethyl acetate yielded crystals of **10**, suitable for an X-ray crystal structure determination.

5.7.1.2. 3,10-Dibenzyl-3,6,6,10,13,13-hexamethyl-1,8-dioxa-4,11-diazacyclotetradecane-2,5,9,12-tetraone (12). According to GP 5, **11** (368 mg, 1 mmol) in dry toluene (50 mL), for 15 min. Yield: 177 mg (34%) of **12**. White solid. Mp 288.1-290.5 °C (decomp). IR: 3520m, 3460vs, 3057w, 2970s, 1744vs, 1660vs, 1527vs, 1483s, 1364s, 1260s, 1236m, 1121vs, 1020w, 719m, 701s. ^{1}H NMR : 1.11, 1.25, 1.46 (3s, 6Me); 3.28-3.38 (m, 2PhC*H*$_2$); 4.09 (s, 2CH$_2$O); 7.07 (s, 2NH); 7.21-7.31 (m, 10 arom. H). ^{13}C-NMR: 21.3, 21.8 (2q, 2*Me*$_2$C); 28.7 (q, 2Me); 39.7 (s, 2Me$_2$*C*); 41.3 (t, 2CH$_2$); 58.4 (s, 2C); 70.2 (t, 2CH$_2$O); 126.1, 127.3, 129.6 (3d, 10 arom. CH); 135.0 (s, 2arom. C); 171.7, 173.2 (2s, 4CO). ESI-MS: 545 (100, [*M*+Na]$^+$).

Recrystallization from DMF/benzene/CH_2Cl_2/hexane/*i*-PrOH yielded crystals of **12**, suitable for an X-ray crystal structure determination.

5.7.1.3. 3,6,6,10,13,13-Hexamethyl-3,10-diphenyl-1,8-dioxa-4,11-diazacyclotetradecane-2,5,9,12-tetraone (24). According to GP6, **21a** (292 mg, 1 mmol) in dry toluene (50 mL), 15 min, (SiO_2, acetone/ CH_2Cl_2 1:60). Yield: 75 mg (30%) of **24**. White solid. Mp 251.6-253.1 °C (decomp). IR: 3526m, 3435vs, 3023w, 2987s, 1736vs, 1665vs, 1519vs, 1384s, 1276s, 1142vs,

1081w, 998s, 770m, 699s. ^{1}H NMR: 1.30, 1.51, 1.60 (3s, 6Me); 4.41-4.61 (m, 2CH_2O); 7.07 (s, 2NH); 7.28-7.42 (m, 10 arom. H). ^{13}C-NMR: 22.6, 24.5 (2q, 2*Me*$_2$C); 25.7 (q, 2Me); 50.6 (s, 2Me$_2$*C*); 56.1 (s, 2C); 70.0 (t, 2CH_2O); 126.4, 127.7, 128.9 (3d, 10 arom. CH); 141.0 (s, 2arom. C); 172.9 173.5 (2s, 4CO). CI-MS: 513 (32), 512 (100, $[M+NH_4]^+$), 495 (28, $[M+H]^+$).
Recrystallization from toluene/MeCN/acetone yielded crystals of **24**, suitable for an X-ray crystal structure determination.

5.7.1.4. Reaction of 22 under DAC conditions. A suspension of **22** (188 mg, 0.5 mmol) in toluene (30 mL) was heated to 100 °C, and dry HCl gas was bubbled through the suspension for 20 min (IR monitoring). Then, the mixture was allowed to cool to rt while bubbling N_2 through it (*ca*. 20 min), MeOH was added to the solution and stirred at rt for 1 h. The solvent was evaporated, the oily residue was purified by CC (AcOEt/hexane 1:10) yielding **27** (13 mg, 9%), **28** (28 mg, 21%) and **29** (36 mg, 30%).

5.7.1.4.1. Methyl 2-(2-benzylacryloylamino)-2-methylpropanoate (28). Colorless oil. IR: 3332m, 3069m, 2954vs, 2861s, 1727vs, 1661s, 1537s, 1454s, 1364m, 1282vs, 1241s, 1144s, 1073s, 1026m, 931w, 731m, 701m. ^{1}H NMR: 1.46, 1.49 (2s, Me$_2$C); 3.61 (s, CH_2); 3.71 (s, MeO); 5.22, 5.79 (2s, H_2C=); 6.32 (br s, NH); 7.14-7.32 (m, Ph). ^{13}C NMR: 24.5 (q, *Me*$_2$C); 38.5 (t, CH_2); 52.4 (s, MeO); 56.4 (s, Me$_2$*C*); 119.6 (t, H_2C=); 126.4, 128.4, 128.8 (3d, 5 arom. CH); 138.2 (s, arom. C); 144.4 (s, *C*=CH_2); 167.3, 174.8 (2s, 2CO). CI-MS: 263 (18), 262 (100, $[M+H]^+$).

5.7.1.4.2. 2-Benzyl-*N*-[1-methyl-1-(*N*-methyl-*N*-phenylcarbamoyl)ethyl]acrylamide (29). White solid. Mp 119.1-121.6 °C. IR: 3282s, 3060w, 2932m, 1634vs, 1598s, 1541s, 1481s, 1421m, 1390s, 1254m, 1172w, 1090s, 1079m, 769m, 703s. ^{1}H NMR: 1.41 (s, Me$_2$C); 3.20 (s, MeN); 3.46 (s, CH_2); 5.10, 5.53 (2s, H_2C=); 6.18 (br s, NH); 7.09-7.39 (m, 2Ph). ^{13}C NMR: 26.1 (q, *Me*$_2$C); 38.4 (t, CH_2); 41.3 (q, MeN); 58.1 (s, Me$_2$*C*); 120.0 (t, H_2C=); 126.5, 127.8, 128.1, 128.6, 129.0, 129.4 (6d, 10 arom. CH); 138.4, 143.4 (2s, 2arom. C); 144.4 (s, *C*=CH_2); 166.5, 173.1 (2s, 2CO). CI-MS: 237 (52, $[M+H]^+$), 230 (100, $[M$-N(Me)Ph$]^+$), 108 (18).

5.7.1.5. 2-(2-Hydroxyphenyl)-4,4-dimethyl-1,3-oxazol-5(4*H*)-one (31). According to GP6, **30** (156 mg, 0.5 mmol) in dry toluene (50 mL), 5 min (SiO_2, acetone/CH_2Cl_2 1:40). Yield: 73 mg (74%) of **31**. Colorless crystals. Mp. 68.2-69.0 °C. IR: 3079m, 2977s, 1823vs, 1643vs, 1615vs, 1579s, 1478s, 1320vs, 1251s, 1206s, 1090s, 1016s, 915s, 735s. ^{1}H NMR: 1.55 (s, Me_2C); 6.84-7.08, 7.41-7.49, 7.68-7.73 (3m, 4arom. H). ^{13}C NMR: 24.8 (q, *Me*$_2$C); 64.5 (s, Me$_2$*C*); 108.8 (s, arom. C); 117.2, 119.3, 128.2, 134.5 (d, 4 arom. CH); 160.0 (s, C=N); 161.8 (s, arom. C); 178.6 (s, CO). CI-MS: 206 (100, $[M+NH_4]^+$). Recrystallization from $CDCl_3/CH_2Cl_2$ yielded crystals of **31**, suitable for an X-ray crystal structure determination.

5.7.1.6. Reaction of 33a under DAC conditions. According to GP6, **33a** (152 mg, 0.5 mmol) in dry toluene (50 mL), 6 min, CC (SiO_2, acetone/CH_2Cl_2 1:10). Yield: 51 mg (34%) of **35a** and 30 mg (28%) of **34a.**

5.7.1.6.1. *N*-[1-Methyl-1-(*N*-methyl-*N*-phenylcarbamoyl)ethyl]cyclopent-1-enecarboxamide (35a). White solid. Mp 109.6-111.1 °C. ^{1}H NMR: 1.53 (s, Me_2C); 1.84-1.95, 2.22-2.26, 2.37-2.44 (3m, 3 CH_2); 3.26 (s, Me_2N); 5.81 (m, CH=); 6.43 (br s, NH); 7.20-7.23, 7.29-7.34 (m, Ph). ^{13}C NMR: 23.4 (t, CH_2); 26.6 (q, *Me*$_2$C); 31.0, 31.1, 32.8 (3t, 3CH_2); 41.3 (q, MeN); 57.7 (s, Me$_2$*C*); 117.9 (s, C=); 127.6, 127.8, 129.1 (d, 5 arom. CH); 139.4 (d, CH=); 144.5 (s, arom. C); 169.0, 173.1 (2s, 2CO). ESI-MS: 202 (100, $[M+Na]^+$).

5.7.1.6.2. 2-(2-Hydroxycyclopentyl)-4,4-dimethyl-1,3-oxazol-5(4*H*)-one (34a). White solid. M.p. 98.0-102.1 °C (decomp). IR: 3080w, 2980m, 1822vs, 1642s, 1597s, 1472m, 1382w, 1216m, 1095s, 1018m, 916s. ^{1}H NMR: 1.56 (s, Me_2C); 1.54-1.75, 1.79-1.98 (2m, 3 CH_2, CH); 4.41 (m, CHO). ^{13}C NMR: 22.4 (t, CH_2); 25.4, 25.8 (2q, *Me*$_2$C); 27.8, 31.1 (3t, 3CH_2); 54.4 (d, CH); 62.3 (s, Me$_2$*C*); 76.1 (d, CHO); 162.5 (s, C=N); 173.1 (s, CO). CI-MS: 229 (100, $[M+NH_4]^+$).

5.7.1.7. Reaction of 33b under DAC conditions. According to GP6, **33b** (158 mg, 0.5 mmol) in dry toluene (50 mL), 6 min, CC (SiO_2, acetone/CH_2Cl_2 1:10). Yield: 51 mg (34%) of **35b** and 31 mg (31%) of **34b.**

5.7.1.7.1. *N*-[1-Methyl-1-(*N*-methyl-*N*-phenylcarbamoyl)ethyl]cyclohex-1-enecarboxamide (35b). White crystals. Mp 112.1-113.8 °C. ^{1}H NMR: 1.46 (s, Me_2C); 1.52-1.62, 1.84-1.96, 2.01-2.14 (3m, $4CH_2$); 3.26 (s, MeN); 5.85 (m, CH=); 6.53 (br s, NH); 7.18-7.20, 7.30-7.36 (m, Ph). ^{13}C NMR: 21.4, 21.9, 23.8, 25.2 (4t, $4CH_2$); 26.6 (q, Me_2C); 41.3 (q, MeN); 57.6 (s, Me_2C); 117.1 (s, CH=); 127.7, 129.1, 129.3 (3d, 5arom. CH); 133.9 (d, CH=); 144.5 (s, arom. C); 169.6, 173.2 (2s, 2CO). ESI-MS: 323 (100, $[M+Na]^+$).

5.7.1.7.2. 2-(2-Hydroxycyclohexyl)-4,4-dimethyl-1,3-oxazol-5(4*H*)-one (34b). White solid. Mp 101.1-105.2 °C (decomp). IR: 3288w, 3017m, 29619m, 1824vs, 1638s, 1595s, 1490m, 1421m, 1380m, 1092s, 917s. ^{1}H NMR: 1.39, 1.43 (2s, Me_2C); 1.44-1.56, 1.64-1.89, 1.90-1.98 (3m, $4CH_2$); 4.01 (m, CHO). ^{13}C NMR: 19.8, 24.9, 26.6 (3t, $3CH_2$); 26.0, 26.1 (q, Me_2C); 31.9 (t, CH_2); 49.0 (d, CH); 64.0 (s, Me_2C); 66.9 (d, CHO); 163.1 (s, C=N); 176.8 (s, CO). CI-MS: 215 (100, $[M+NH_4]^+$).

5.7.2. Other cyclizations

5.7.2.1. *trans*-3,10-Dibenzyl-6,6,13,13-tetramethyl-1,8-dioxa-4,11-diazacyclotetradecane-2,5,9,12-tetraone (*trans*-**14**). According to GP7, **15** (321 mg, 1 mmol) or **13** (279 mg, 1 mmol). Yield of *trans*-**14**: 108 mg (44%) (from **13**) and 60 mg (24%) (from **15**), respectively. Colorless crystals. M.p. 232.9-234.6 °C (decomp). $[\alpha]_D^{25} = 0$ (c = 1, $CHCl_3$). IR: 3374vs, 3024w, 2966m, 1732vs, 1645vs, 1531s, 1366m, 1282s, 1179s, 1108w, 1001m, 751m, 700m. ^{1}H NMR: 0.90, 0.98 (2s, Me_2C); 3.06 (d, J = 5.8 Hz, CH_2); 3.91-3.96 (m, CH_2); 4.80-4.84 (m, CH); 5.89 (d, J = 3.9 Hz, NH); 6.97-6.99 (m, 6arom. H); 7.10-7.25 (m, 4arom. H). ^{13}C NMR: 21.6, 22.7 (2q, Me_2C); 37.6 (t, $2CH_2$); 42.2 (s, 2C); 52.5 (d, 2CH); 70.9 (t, $2CH_2O$); 127.2, 128.6, 129.3 (3d, 10 arom. CH); 135.7 (s, 2arom. C); 170.0, 174.0 (2s, 4CO). ESI-MS: 517 (100, $[M+Na]^+$), 444 (11). CI-MS: 513 (30), 512 (100, $[M+NH_4]^+$), 496 (12), 495 (30, $[M+H]^+$). Anal. calcd for $C_{28}H_{34}N_2O_6$ (494.59): C 68.00, H 6.93, N 5.66; found: C 67.69, H 7.08, N 5.48.

Recrystallization from *i*-PrOH/CH_2Cl_2/hexane yielded crystals of *trans*-**14**, suitable for an X-ray crystal structure determination.

According to GP8, *rac*-**16** (287 mg, 1 mmol), CC (CH_2Cl_2/acetone 200:1) yielded *trans*-**14** as white crystals in 25% yield (62 mg). $[\alpha]_D^{25} = 0$ (c = 1, $CHCl_3$).

5.7.2.2. *cis*-(*S,S*)-3,10-Dibenzyl-6,6,13,13-tetramethyl-1,8-dioxa-4,11-diaza-cyclotetradecane-2,5,9,12-tetraone ((*S,S*)-14). According to GP8, ***(S)*-16** (1 mmol, 287 mg), CC (CH_2Cl_2/acetone 200:1). Yield 54 mg (22%) of (*S,S*)-**14b.** Mp 212.1-214.4 °C (decomp). $[\alpha]_D^{25}$ = -26.3 (c = 1, $CHCl_3$). ^{1}H NMR: 0.88, 1.08 (2s, $2Me_2C$); 3.13 (s, $2CH_2O$); 3.91-4.04, 4.11-4.22 (2m, $2CH_2$); 4.83-5.00 (m, 2CH); 5.83 (br s, 2NH); 7.03-7.14, 7.28-7.42 (2m, 2Ph). ^{13}C-NMR: 21.5, 22.7 (2q, $2Me_2C$); 37.6 (t, $2CH_2$); 42.1 (s, 2C); 53.3 (d, 2CH); 71.0 (t, $2CH_2$); 127.3, 128.7, 129.4 (3d, 10 arom. CH); 136.1 (s, 2arom. C); 169.7, 174.3 (2s, 4CO). ESI-MS: 517 (100, $[M+Na]^+$), 444 (11). Recrystallization from CH_2Cl_2/*sec*-BuOH yielded crystals of *(S,S)*-**14**, suitable for an X-ray crystal structure determination.

5.8. X-Ray crystal structure determination of 10, 11a, 12, *trans*-14, *(S,S)*-14, 24 and 31

All measurements were made on a *Nonius KappaCCD* area-detector diffractometer[34] using graphite-monochromated MoK_α radiation (λ 0.71073 Å) and an *Oxford Cryosystems Cryostream 700* cooler. The data collection and refinement parameters are given below[35] and views of the molecules are shown in Figures 1-3. Data reduction was performed with *HKL Denzo* and *Scalepack*.[36] The intensities were corrected for Lorentz and polarization effects, but not for absorption. Equivalent reflections were merged. Each structure was solved by direct methods using *SIR92*,[37] which revealed the positions of all non-hydrogen atoms.

In the case of **10, 12,** *trans*-**14** and **24,** the molecule sits about a crystallographic centre of inversion.

In the case of (*S,S*)-**14**, there are two symmetry-independent molecules in the asymmetric unit. The atomic coordinates of the two molecules were tested carefully for a relationship from a higher symmetry space group using the program *PLATON*,[38] but none could be found. The crystal is merohedrally twinned. Successful refinement of the structure was achieved using the

twin operator [1 0 0 / 0 -1 0 / 0 0 -1] and the major twin domain has a volume fraction of 0.640(1).

The non-hydrogen atoms were refined anisotropically. Any amide or hydroxy H-atoms in the structures were placed in the positions indicated by a difference electron density map and their positions were allowed to refine together with inividual isotropic displacement parameters. All remaining H-atoms were placed in geometrically calculated positions and refined using a riding model where each H-atom was assigned a fixed isotropic displacement parameter with a value equal to $1.2U_{eq}$ of its parent C-atom ($1.5U_{eq}$ for the methyl groups). Except for **11a**, the refinement of each structure was carried out on F^2 by using full-matrix least-squares procedures, which minimised the function $\Sigma w(F_o^2 - F_c^2)^2$. The refinement of the structure of **11a** was carried out on F by minimizing the corresponding function based of F. Corrections for secondary extinction were applied.

Neutral atom scattering factors for non-hydrogen atoms were taken from Ref. 39, and the scattering factors for H-atoms were taken from Ref. 40. Anomalous dispersion effects were included in F_C,[41] the values for f' and f'' were those of Ref. 42. The values of the mass attenuation coefficients are those of Ref. 43. All calculations were performed using the *SHELXL97* program[44] with the exception of **11a,** where the *teXsan* crystallographic software package[45] was used.

Crystal data for **10.** $C_{22}H_{34}N_2O_6$, M = 422.52, colorless, plate, crystal dimensions 0.05 × 0.12 × 0.30 mm, triclinic, space group $P\bar{1}$, Z = 1, reflections for cell determination 2354, 2θ range for cell determination 4 – 55°, a = 6.0630(5) Å, b = 9.5495(6) Å, c = 10.7064(9) Å, α = 66.451(3)°, β = 83.228(4)°, γ = 71.733(5)°, V = 539.61(7) Å^3 , T = 160 K, D_x = 1.300 g cm^{-3}, μ(MoK_α) = 0.0941 mm^{-1}, $2\theta_{(max)}$ = 55°, total reflections measured = 11110, symmetry independent reflections = 2457, reflections with $I > 2\sigma(I)$ = 1919, reflections used in refinement = 2455, parameters refined = 143, $R(F)$ [$I > 2\sigma(I)$ reflections] = 0.0473, $wR(F^2)$ [all data] = 0.1277 (w = $[\sigma^2(F_o^2) + (0.0624P)^2 + 0.093P]^{-1}$ where P = $(F_o^2 + 2F_c^2) / 3$), goodness of fit = 1.059,

secondary extinction coefficient = 0.09(2), final Δ_{max}/σ = 0.001, $\Delta\rho$ (max; min) = 0.30; -0.28*e* Å^{-3}.

Crystal data for **11a.** $C_{17}H_{26}N_2O_3$, M = 306.40, colorless, prism, crystal dimensions 0.15 × 0.15 × 0.25 mm, monoclinic, space group $P2_1/n$, Z = 4, reflections for cell determination 4110, 2θ range for cell determination 4 – 55°, a = 8.1009(1) Å, b = 17.1770(3) Å, c = 12.6459(2) Å, β = 101.112(1)°, V = 1726.67(5) Å^3 , T = 160 K, D_x = 1.179 g cm^{-3}, μ(MoK_α) = 0.0806 mm^{-1}, $2\theta_{(max)}$ = 55°, total reflections measured = 37684, symmetry independent reflections = 3973, reflections used in refinement [$I > 2\sigma(I)$] = 2947, parameters refined = 208, *R(F)* = 0.0469, *wR(F)* = 0.0469 ($w = [\sigma^2(F_o) + (0.005F_o)^2]^{-1}$, goodness of fit = 2.962, secondary extinction coefficient = 3.3(5) × 10^{-6}, final Δ_{max}/σ = 0.0005, $\Delta\rho$ (max; min) = 0.39; -0.27*e* Å^{-3}.

Crystal data for **12.** $C_{30}H_{38}N_2O_6$, M = 522.64, colorless, tablet, crystal dimensions 0.05 × 0.10 × 0.20 mm, monoclinic, space group $P2_1/n$, Z = 2, reflections for cell determination 2439, 2θ range for cell determination 4 – 50°, a = 6.0109(2) Å, b = 17.3238(5) Å, c = 12.9060(5) Å, β = 91.855(2) °, V = 1343.22(8) Å^3 , T = 160 K, D_x = 1.292 g cm^{-3}, μ(MoK_α) = 0.0896 mm^{-1}, $2\theta_{(max)}$ = 50°, total reflections measured = 17323, symmetry independent reflections = 2359, reflections with $I > 2\sigma(I)$ = 1731, reflections used in refinement = 2358, parameters refined = 180, *R(F)* [$I > 2\sigma(I)$ reflections] = 0.0540, *wR(F^2)* [all data] = 0.1283 ($w = [\sigma^2(F_o^2) + (0.0395P)^2 + 0.6836P]^{-1}$ where $P = (F_o^2 + 2F_c^2) / 3$), goodness of fit = 1.129, secondary extinction coefficient = 0.013(2), final Δ_{max}/σ = 0.001, $\Delta\rho$ (max; min) = 0.35; -0.18*e* Å^{-3}.

Crystal data for *trans*-**14.** $C_{28}H_{34}N_2O_6$, M = 494.58, colorless, needle, crystal dimensions 0.05 × 0.05 × 0.25 mm, monoclinic, space group $C2/c$, Z = 4, reflections for cell determination 2421, 2θ range for cell determination 4 – 50°, a = 18.6829(6) Å, b = 14.5471(5) Å, c = 10.0381(3) Å, β = 104.943(2)°, V = 2635.9(2) Å^3 , T = 160 K, D_x = 1.246 g cm^{-3}, μ(MoK_α) = 0.0875 mm^{-1}, $2\theta_{(max)}$ = 50°, total reflections measured = 18709, symmetry independent reflections = 2333, reflections with $I > 2\sigma(I)$ = 1579, reflections used in refinement = 2333, parameters refined = 170, *R(F)* [$I >$

$2\sigma(I)$ reflections] = 0.0456, *wR(F²)* [all data] = 0.1156 ($w = [\sigma^2(F_o^2) + (0.041P)^2 + 1.0127P]^{-1}$ where $P = (F_o^2 + 2F_c^2)/3$), goodness of fit = 1.040, secondary extinction coefficient = 0.0040(7), final Δ_{max}/σ = 0.001, $\Delta\rho$ (max; min) = 0.18; -0.17*e* Å^{-3}.

Crystal data for (*S*,*S*)-**14.** $C_{28}H_{34}N_2O_6$, *M* = 494.58, colorless, prism, crystal dimensions 0.13 × 0.13 × 0.30 mm, monoclinic, space group $P2_1$, *Z* = 4, reflections for cell determination 7591, 2θ range for cell determination 4 – 60°, *a* = 5.4181(2) Å, *b* = 35.569(1) Å, *c* = 13.3108(4) Å, β = 90.090(1)°, *V* = 2565.2(2) Å^3 , *T* = 160 K, D_x = 1.281 g cm^{-3}, μ(MoK_α) = 0.0899 mm^{-1}, $2\theta_{(max)}$ = 60°, total reflections measured = 52489, symmetry independent reflections = 7611, reflections with $I > 2\sigma(I)$ = 5073, reflections used in refinement = 7606, parameters refined = 675, *R(F)* [$I > 2\sigma(I)$ reflections] = 0.0446, *wR(F²)* [all data] = 0.0899 ($w = [\sigma^2(F_o^2) + (0.036P)^2]^{-1}$ where $P = (F_o^2 + 2F_c^2)/3$), goodness of fit = 1.025, secondary extinction coefficient = 0.012(1), final Δ_{max}/σ = 0.001, $\Delta\rho$ (max; min) = 0.23; -0.21*e* Å^{-3}.

Crystal data for **24.** $C_{28}H_{34}N_2O_6$, *M* = 494.58, colorless, prism, crystal dimensions 0.22 × 0.25 × 0.32 mm, triclinic, space group $P\bar{1}$, *Z* = 1, reflections for cell determination 2078, 2θ range for cell determination 4 – 50°, *a* = 5.9467(3) Å, *b* = 10.1233(5) Å, *c* = 10.9664(5) Å, α = 73.363(3)°, β = 83.818(3)°, γ = 76.704(3)°, *V* = 614.97(5) Å^3 , *T* = 160 K, D_x = 1.335 g cm^{-3}, μ(MoK_α) = 0.0938 mm^{-1}, $2\theta_{(max)}$ = 50°, total reflections measured = 8138, symmetry independent reflections = 2137, reflections with $I > 2\sigma(I)$ = 1796, reflections used in refinement = 2136, parameters refined = 171, *R(F)* [$I > 2\sigma(I)$ reflections] = 0.0390, *wR(F²)* [all data] = 0.1010 ($w = [\sigma^2(F_o^2) + (0.043P)^2 + 0.2587P]^1$ where $P = (F_o^2 + 2F_c^2)/3$), goodness of fit = 1.067, secondary extinction coefficient = 0.052(9), final Δ_{max}/σ = 0.001, $\Delta\rho$ (max; min) = 0.18; -0.25*e* Å^{-3}.

Crystal data for **31.** $C_{11}H_{11}NO_3$, M = 205.21, colorless, prism, crystal dimensions 0.10 × 0.17 × 0.30 mm, monoclinic, space group $P2_1/n$, Z = 4, reflections for cell determination 2470, 2θ range for cell determination 4 – 55°, a = 5.6230(2) Å, b = 8.9884(4) Å, c = 20.2034(8) Å, β = 93.985(3)°, V = 1018.65(7) Å^3 , T = 160 K, D_x = 1.338 g cm^{-3}, μ(Mo$K\alpha$) = 0.0982 mm^{-1}, $2\theta_{(max)}$ = 55°, total reflections measured = 21205, symmetry independent reflections = 2333, reflections with $I > 2\sigma(I)$ = 1834, reflections used in refinement = 2331, parameters refined = 143, $R(F)$ [$I > 2\sigma(I)$ reflections] = 0.0517, $wR(F^2)$ [all data] = 0.1359 ($w = [\sigma^2(F_o^2) + (0.0581P)^2 + 0.2986P]^{-1}$ where $P = (F_o^2 + 2F_c^2)/3$), goodness of fit = 1.107, secondary extinction coefficient = 0.032(6), final Δ_{max}/σ = 0.001, $\Delta\rho$ (max; min) = 0.21; -0.22e Å^{-3}.

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References and notes

1. Iliev, B.; Linden, A.; Heimgartner, H. *Helv. Chim. Acta* **2003,** *86,* 3215-3234.
2. Obrecht, D.; Heimgartner, H. *Helv. Chim. Acta* **1984,** *67*, 526-533.
3. Obrecht, D.; Heimgartner, H. *Helv. Chim. Acta* **1987,** *70*, 329-338.
4. Obrecht, D.; Heimgartner, H. *Helv. Chim. Acta* **1990,** *73*, 221-228.
5. Villalgordo, J. M.; Heimgartner, H. *Helv. Chim. Acta* **1997,** *80,* 748-766.
6. Koch, K. N.; Linden, A.; Heimgartner, H. *Helv. Chim. Acta* **2000,** *83,* 233-257.
7. Koch, K. N.; Linden, A.; Heimgartner, H. *Tetrahedron* **2001,** *57,* 2311-2326.
8. Heimgartner, H.; Arnhold, F. S.; Fritschi, S.; Koch, K. N.; Linden, A.; Magirius, J. E. F. *J. Heterocycl. Chem.* **1999,** *36,* 1539-1547.

9. Linden, A.; Ghorbani-Salman Pour, F.; Breitenmoser, R. A.; Heimgartner, H. *Acta Crystallogr., Sect. C* **2001,** *57*, 634-637.
10. Richard, S.; Prie, G.; Guignard, A.; Thibonet, J.; Luc Parrain, J.; Duchene, A.; Abarbri, M. *Helv. Chim. Acta* **2003,** *86*, 726-732.
11. Wasserman, H.; Keggi, J.; McKeon, J. *J. Am. Chem. Soc*. **1961**, *83*, 4107-4108.
12. Wasserman, H.; Keggi, J.; McKeon, J. *J. Am. Chem. Soc*. **1962**, *84*, 2978-2982.
13. Shemyakin, M. M.; Antonov, V. K.; Shkrob, A. M.; Schelokov, V. I.; Agadzhanyan, Z. E. *Tetrahedron* **1965,** *21*, 3537-3572.
14. Matsuyama, T.; Bhasin, A.; Harshey, R. *J. Bacteriol.* **1995**, *177*, 987-991.
15. Strobel, G.; Morrison, S.; Cassella, M. *U.S. Patt. Appl. Publ.* **2003**, US2001-858871.
16. Hassall, C.; Martin, T.; Schofield J. *Tetrahedron Lett.* **1964**, *5*, 3741-3743.
17. Hassall, C.; Martin, T.; Schofield J. *J. Chem. Soc. Sect.C* **1967**, *32*, 997-1003.
18. Ovchinnikov, Y.; Ivanov, V.; Kiryushkin, A.; Shemyakin, M. *Doklady Akademii Nauk SSSR* **1963**, *153*, 122-125.
19. Philipova, I.; Linden, A.; Heimgartner, H. *Helv. Chim. Acta* **2005,** *88*, 1711-1733.
20. Stoykova, S. A. PhD Thesis, University of Zurich, 2004.
21. Heimgartner, H. *Angew. Chem. Int. Ed.* **1991,** *30*, 238-265.
22. The crystal structure of **11a** was established by X-ray crystallography (see exptl. part). Since the space group is centrosymmetric, the crystals are racemic. The *trans*-amide group is planar. The amide NH group forms an intramolecular hydrogen bond with the hydroxy O-atom, while the hydroxy group forms an intermolecular hydrogen bond with the O-atom of the amide group in the centre of the molecule of a neighboring molecule, thereby linking the molecules into extended chains.
23. Johnson, C. K. *ORTEPII, Report ORNL-5138*, Oak Ridge National Laboratory, Oak Ridge, Tennessee, 1976.
24. Bernstein, J.; Davis, R. E.; Shimoni, L.; Chang, N.-L. *Angew. Chem.* **1995**, *107*, 1689-1708; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1555-1573.
25. Wipf, P.; Heimgartner, H. *Helv. Chim. Acta* **1987**, *70*, 354-368.
26. Fujita, T.; Hanyu, N.; Mino, T.; Sakamoto, M. *Synthesis* **2001,** *12*, 1846-1851.
27. Geffken, D. *Arch. Pharm.* **1979**, *312*, 360-361.

28. Monteil, T.; Danvy, D.; Plaquevent, J.; Duhamel, L.; Duhamel, P.; Gros, C.; Schwartz, J.; Lecomte, J. *Synth. Commun.* **2001**, *31*, 211-218.
29. Obrecht, D.; Heimgartner, H. *Chimia* **1982,** *36*, 78-81.
30. Dewar, M. J.; Zoebisch, E. G.; Healy, E. F.; Stewart, J. P. *J. Am. Chem. Soc.* **1985,** *107*, 3902-3909.
31. AMPAC 6.5.5, Semichem Inc., 7128 Summit, Shawnee, KS66216
32. Herradon, D.; Seebach, D. *Helv. Chim. Acta* **1989**, *72*, 690-714.
33. Seebach, D.; Zimmermann, J. *Helv. Chim. Acta* **1986**, *69*, 1147-1152.
34. Hooft, R. *KappaCCD Collect Software*, Nonius BV, Delft, The Netherlands, 1999.
35. CCDC 284106 – 284112 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via http://www.ccdc.cam.ac.uk/data_request/cif.
36. Otwinowski, Z.; Minor, W. In Carter C. W., Jr.; Sweet, R. M., Eds.; Methods in Enzymology, Vol. 276, Macromolecular Crystallography, Part A, Academic Press: New York, 1997, pp. 307-326.
37. Altomare, A.; Cascarano, G.; Giacovazzo, C.; Guagliardi, A.; Burla, M. C.; Polidori, G.; Camalli, M. *SIR92, J. Appl. Crystallogr.* **1994**, *27*, 435.
38. Spek, A. L. *PLATON, Program for the Analysis of Molecular Geometry*, University of Utrecht, The Netherlands, 2003.
39. Maslen, E. N.; Fox, A. G.; O'Keefe, M. A. In Wilson, A. J. C., Ed.; International Tables for Crystallography; Kluwer Academic: Dordrecht, 1992, Vol. C, Table 6.1.1.1, pp. 477-486.
40. Stewart, R. F.; Davidson, E. R.; Simpson, W. T. *J. Chem. Phys.* **1965**, *42*, 3175-3187.
41. Ibers, J. A.; Hamilton, W. C. *Acta Crystallogr.* **1964**, *17*, 781-782.
42. Creagh, D. C.; McAuley, W. J. In Wilson, A. J. C., Ed.; International Tables for Crystallography; Kluwer Academic: Dordrecht, 1992, Vol. C. Table 4.2.6.8, pp. 219-222.
43. Creagh, D. C.; Hubbell, J. H. In Wilson, A. J. C., Ed.; International Tables for Crystallography; Kluwer Academic: Dordrecht, 1992, Vol. C.. Table 4.2.4.3, pp. 200-206.
44. Sheldrick, G. M. *SHELXL97, Program for the Refinement of Crystal Structures*, University of Göttingen, Germany, 1997.
45. *teXsan: Single Crystal Structure Analysis Software*, Version 1.10, Molecular Structure Corporation, The Woodlands, Texas, 1999.

Chapter 3

Reaction of γ-Hydroxy-*N*-[1-(dimethylcarbamoyl)ethyl] butanamides under the 'Direct Amide Cyclization' Conditions [1])

The preparation of the title compounds was achieved *via* the 'azirine/oxazolone method' starting from the corresponding γ-hydroxy acids. Upon subjecting the γ-hydroxy-*N*-[1-(dimethylcarbamoyl)ethyl]butanamides **4** to the 'Direct Amide Cyclization' (DAC) conditions, chlorinated acids **11** or imino lactones **12** were obtained as the sole products instead of the expected cyclodepsipeptides **A** or their cyclodimers (*Scheme 4)*. Variation of the substituents in **4** did not affect the outcome of the reaction and a mechanism for the formation of both products from the intermediate oxazolone **13** has been proposed. Under the acidic conditions of the DAC, the imino lactones are formed as their HCl salts **12**, which, in polar solvents or on silicagel, react further to give the chlorinated acids **11**. Stabilization of the imino lactones was achieved by increasing the substitution in the five membered ring and their structure, in the form of the hydrochlorides, was proven independently by X-ray crystallography (*Fig*. *4*). A derivative **15** of the imino lactone **12a** was prepared by the reaction with the 2*H*-azirin-3-amine **10a**; its structure was also established by an X-ray crystal-structure determination (*Fig. 3*). Furthermore, the structures of the ω-chloro acids **11a** and **11b** were determined by X-ray crystallography (*Fig*. *2*).

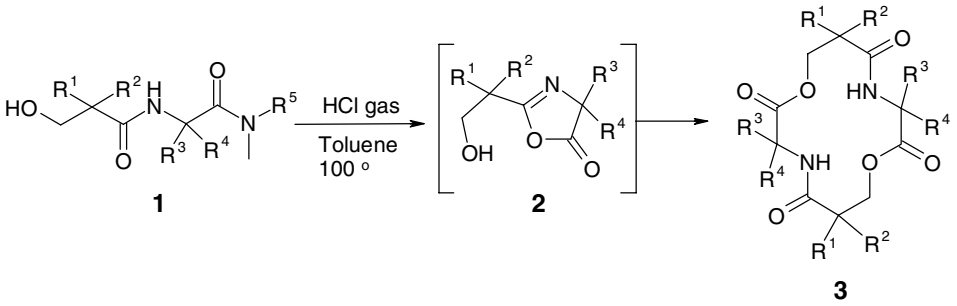
[1]) B. Iliev, A. Linden, H. Heimgartner, *Helv. Chim. Acta*, submitted.

1. Introduction

Cyclic depsipeptides, *i.e.* heterodetic cyclopeptides which contain ester (depside) bonds as part of their backbone, have been found in many natural products, and show a wide spectrum of biological activity [1]. They are therefore sought after as promising lead compounds for drug design and discovery. Nature is a rich source of fascinating cyclodepsipeptides, and although the significance of incorporating a depside bond is still not clear, it appears to be essential for biological activity, since all-amide analogues are often inactive [2]. The depside bond is recognized as being more difficult to incorporate into the backbone than the amide bond, although macrolactonizations have been studied extensively [2-6], and is therefore usually pre-formed in the linear precursor prior to the cyclization *via* amide bond formation to give cyclic depsipeptides.

The most-well-known structures in this class of natural products belong to the ion-selective antibiotics, such as valinomycin [7], the closely related enniatin family [8], the actinomycins [9], and others. The reduction in the conformational freedom brought about by cyclization often results in higher receptor binding affinity. Frequently in these cyclic compounds, extra conformational restrictions are also built in, such as D-amino acids, *N*-alkylated-amino acids or α,α-disubstituted amino acids.

A very efficient method for the incorporation of the latter into depsipeptide rings, the so called 'direct amide cyclization' (DAC), has been developed in our research group in recent years. It has been used successfully for the synthesis of 6-, 9-, 12- and 15-membered cyclodepsipeptides from α-hydroxy acids [10-12], as well as larger ring systems from α- and β-hydroxy acids [13-15]. Therefore, we were interested to investigate reactions of depsipeptides containing β-, γ- and δ-hydroxy acids and an α-amino acid with the aim of synthesizing 7- to 9-membered analogues. As we reported earlier, the cyclization of β-hydroxy acid amides **1**, the linear precursors of the desired 7-membered rings, yielded only cyclodimers **3** by the dimerization process [16][17] (*Scheme 1, Table 1*).



Scheme 1

Monosubstitution at C(α) of the amino acid moiety (R^3=H) did not prevent twinning, although the cyclization was carried out under different conditions [17][3]). If, however, the hydroxy acid moiety in **1** was monosubstituted at C(α), no cyclic depsipeptides were obtained, although the formation of the intermediate 1,3-oxazol-5(4*H*)-one **2** has been monitored by IR spectroscopy. Instead, water elimination occurred, to give derivatives of α,β-unsaturated acid amides.

In the present paper, we describe the results of reactions of the higher homologues of **1** containing γ-hydroxy acids, which were carried out with the aim of obtaining either 8- or 16-membered cyclodepsipeptides.

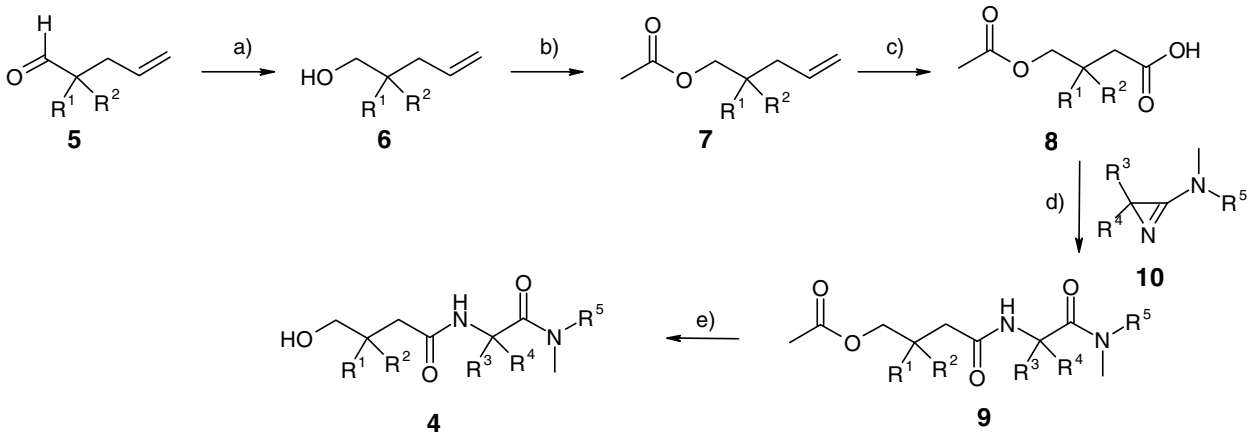
2. Results and Discussion

The linear amides **4** were synthesized in five steps from the γ,δ-unsaturated aldehydes **5** (*Scheme 2*). Reduction gave the pentenols **6**, which were acetylated to give **7**[4]). The introduction of the carboxyl group was achieved by oxidative cleavage of the C=C bond of **7,** either with

[3]) The DAC conditions were not applicable in this case because of the sluggish formation of the 1,3-oxazol-5(4*H*)-one intermediate (cf. [18]).

[4]) The need for protection of the hydroxy group arises from the fact that attempts to obtain the desired γ-hydroxy acids from the corresponding easily available lactones (*e.g.* 4,4-dimethyltetrahydropyran-2-one) by alkaline hydrolysis failed. Upon acidification of the sodium salt, spontaneous lactonization occurred and only the starting lactone could be isolated.

Ru(IV)oxide/$NaIO_4$ [19] or with oxone/acetone [20], although purification proved to be easier in the first case, thus leading to **8** in higher yields. The protection of the hydroxy group prevents the formation of the lactone under these oxidation conditions [21]. The coupling of **8** with the respective amino acid to give **9** was performed by the reaction with 2,2,*N*,*N*-tetramethyl- or 2,2,*N*-trimethyl-*N*-phenyl-2*H*-azirine-3-amine (**10a, 10b**) and *N*,*N*-dimethyl-1-azaspiro[2.4]hept-1-en-2-amine (**10c**), respectively, at room temperature ('azirine/oxazolone method' [22][23]). Deprotection of the hydroxy group by treatment with LiOH in THF/H_2O led to the linear precursors **4.**



a) $NaBH_4$,MeOH, 0°, 1 h; b) Ac_2O, Pyr, Et_2O, reflux, 1 h; c) $NaIO_4$, Ru(IV)oxide, MeCN,CCl_4, H_2O, r.t.,14 h; d) **10,** THF, r.t., 24 h; e) LiOH, THF/H_2O, r.t., 2 h.

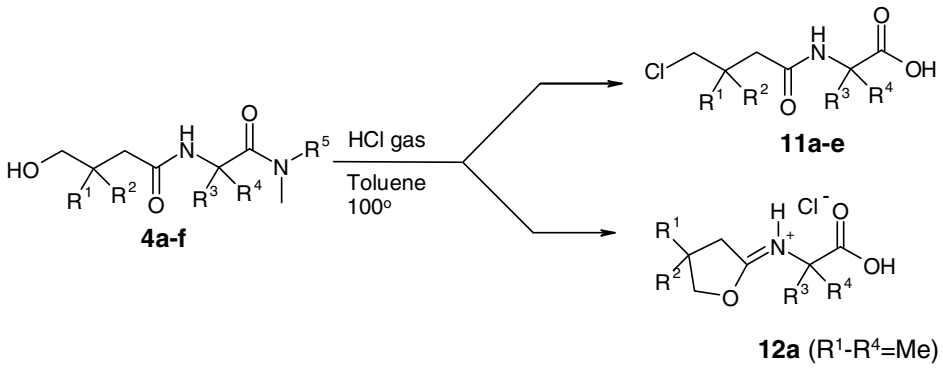
Scheme 2

	4a/11a	**4b/11b**	**4c/11c**	**4d/11a**	**4e/11d**	**4f/11e**
R^1	Me	H	Me	Me	H	Me
R^2	Me	H	Me	Me	Ph	Ph
R^3	Me	Me	$-CH_2-CH_2$	Me	Me	Me
R^4	Me	Me	$-CH_2-CH_2$	Me	Me	Me
$R^{5\,a)}$	Me	Me	Me	Ph	Ph	Ph

[a)] R^5 only in **4.**

Table 1. *Synthesized γ-Hydroxyamides* **4** *and Chlorinated Acids* **11**

Unexpectedly, the reactions of **4a-c** (*Table 1*) under the conditions of the 'direct amide cyclization' yielded neither the 8-membered nor the 16-membered cyclodepsipeptides. Instead, after chromatographic workup, the chlorinated acids **11a-c** were isolated as the sole products (*Scheme 3*). If the *N*-methyl-*N*-phenylamide **4d** was used instead of the *N,N*-dimethylamides **4a-c,** the formed product could be isolated after evaporation of the solvent and washing of the residue with CH_2Cl_2. The isolated product was identified as the imino lactone hydrochloride **12a** (*Scheme 3*).



Scheme 3

At first it seems that R^5 is determining the product of the reaction. Indeed, it has been shown that in some DAC reactions *N,N*-dimethyl- and *N*-methyl-*N*-phenyl amides behave quite differently [15]. Therefore, the cyclization of **4e** and **4f** was attempted under DAC conditions. Surprisingly, in both cases the product was not the imino lactone of type **12,** but the chlorinated acid of type **11**. Therefore, the presence of the PhN residue is not the reason for the different behavior of **4d** under DAC conditions.

The explanation lies in the purification process. Since *N*-methylaniline hydrochloride is soluble in CH_2Cl_2 [16][17] and the products of the reaction are not, the crude residue in the case of **4d** was just washed with CH_2Cl_2, and thus the imino lactone was isolated as its hydrochloride **12a** in pure form. On the other hand, $Me_2NH.HCl$ is insoluble in CH_2Cl_2, so that chromatographic workup was necessary in the case of **4a-c**, which led to the formation of the corresponding chloro acids **11**. In the case of **4e,f**, due to the presence of the Ph substituent in the hydroxy acid moiety, the product of the reaction was soluble in CH_2Cl_2 and no precipitate was formed. For this reason,

chromatographic purification was required which yoelded chlorinated acids **11** as the sole product (*Scheme 3*).

It is worth mentioning, that the ^{1}H-NMR spectrum of **12a** in (D_6)DMSO changes with time. After just half an hour at room temperature, the appearance of signals at 1.00, 1.31, 2.09, 3.59 and 8.05 ppm was observed, which grew stronger with time, while the signals at 1.15, 1.56, 3.13 and 4.56 ppm diminish (*Fig. 1)*.

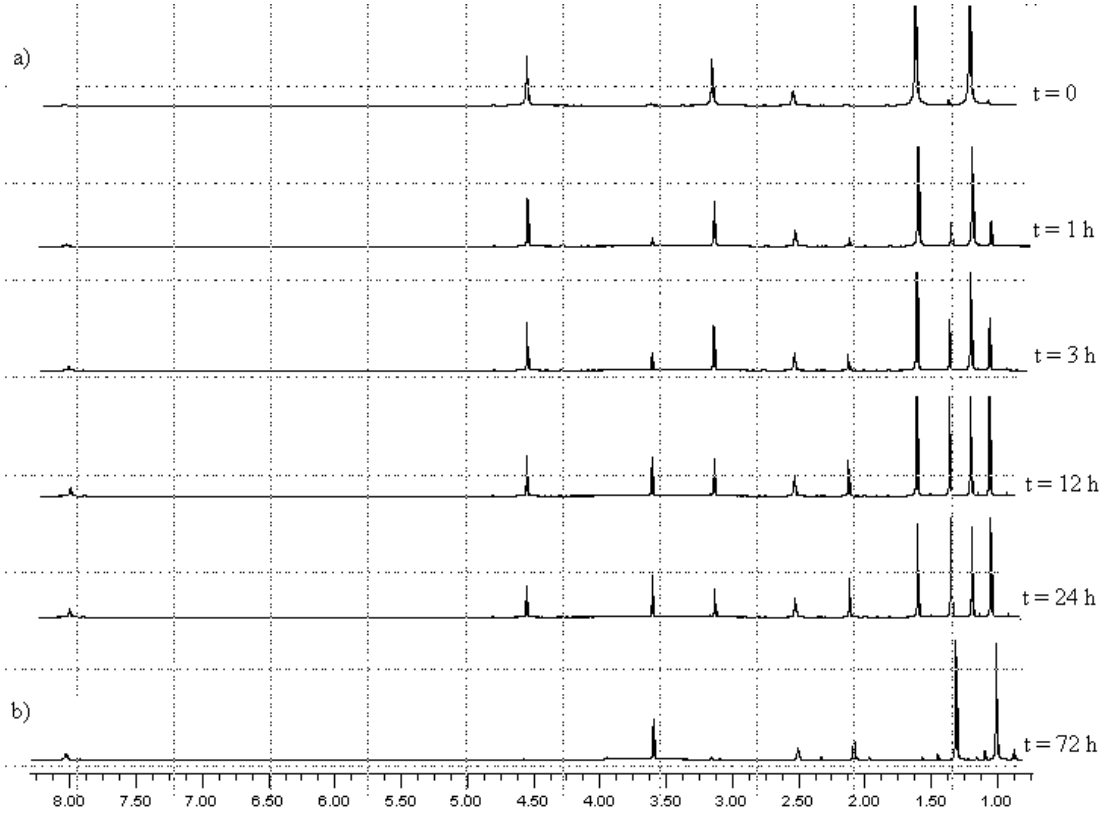
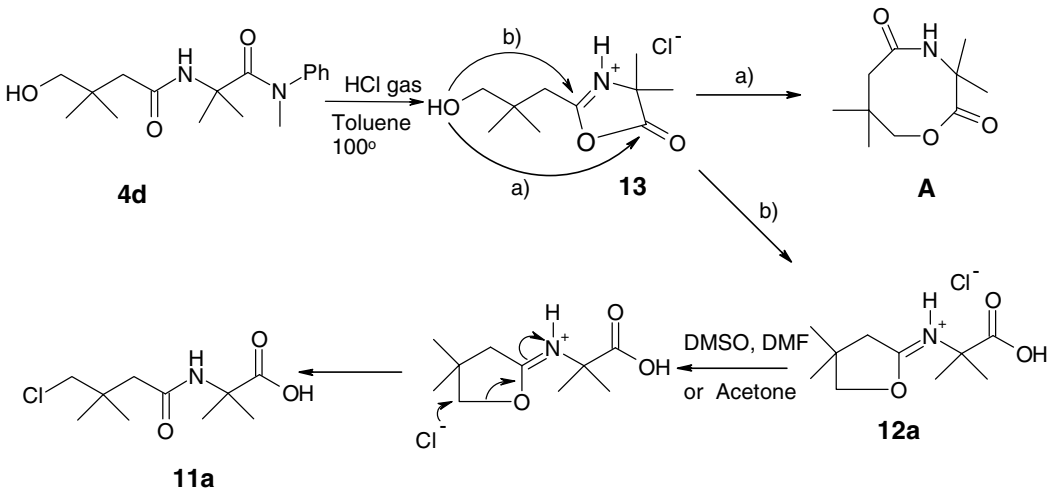


Fig. 1. *Dynamic ^{1}H-NMR spectrum of* **12a** *in (D_6)DMSO: a) Spectrum of* **12a**, *b) Spectrum of* **11a**

The new signals were sharp and well defined, indicating the formation of a single compound, rather than decomposition. After *ca.* 12 h at room temperature, the ratio of both compounds was roughly 1:1, while after 3 d only traces of the starting compound **12a** could be observed. The spectrum of the newly formed substance coincides with the spectrum of **11a**. The same process was also observable in the ^{13}C NMR spectrum, the isomerization proceeding in a variety of polar

solvents such as DMF and acetone. In the latter, the ratio between **12a** and **11a** reached 1:1 in about a week and then remained constant. Flash chromatography of a mixture of **11a** and **12a** allowed the isolation of analytical amounts of **12a**. Finally, the instability of **12a** in solution was proven in a control experiment in which a mixture of **12a** and **11a** in CH_2Cl_2 containing 10% of MeOH was stirred at room temperature. After 14 h, only the chlorinated acid **11a** was isolated. Apparently, under the DAC reaction conditions, the initially formed product is the imino lactone hydrochloride **12a**, which, in polar solvents, undergoes an isomerization to give **11a** (*Scheme 4*).



Scheme 4

A reaction mechanism for the formation of **11a** and **12a** is shown in *Scheme 4*. Treatment of **4d** with HCl gas leads to the corresponding 1,3-oxazol-5(4*H*)-one **13**. When no external nucleophiles are present, the OH group acts as a nucleophile and attacks one of the two electrophilic centres in the ring. If the attack occurs at the C=O group (pathway a), the 8-membered cyclodepsipeptide **A** would be formed. On the other hand, the OH attack at the C=N group (pathway b), would lead to the opening of the oxazolone ring yielding the imino lactone hydrochloride **12a**. The latter can be isolated if no chromatographic workup is necessary. In a polar solvent, the chloride ion

apparently attacks the methylene group adjacent to the O-atom, which leads to the open chain ω-chloro acid **11a**[5]).

Due to its instability in solution, no crystals of **12a** suitable for an X-ray crystal structure determination could be obtained, but the structures of the chlorinated acids **11a** and **11b** were confirmed by X-ray crystallography (*Fig. 2*)[6]).

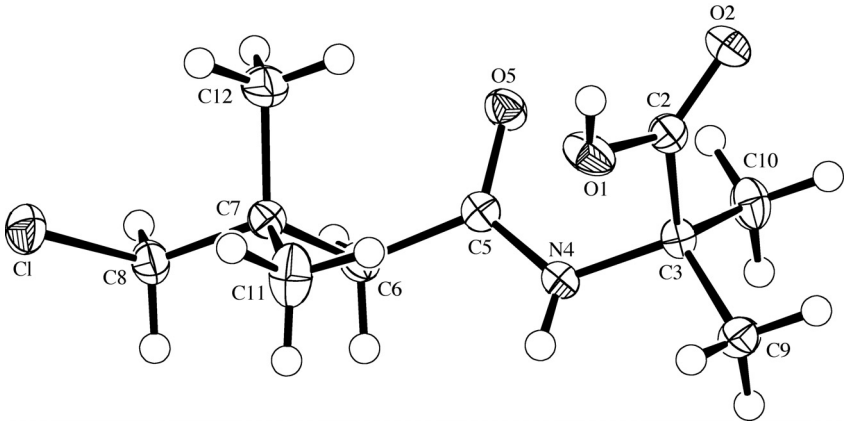
The OH group in **11a** forms an intermolecular H-bond with the amide O-atom of a neighboring molecule, thereby linking the molecules into extended chains which run parallel to the [0 1 0] direction and can be described by a graph set motif [25] of C(7). The amide group forms an intermolecular H-bond with the carboxylate carbonyl O-atom of a different neighboring molecule, thus also linking the molecules into extended chains. These chains run parallel to the [1 0 0] direction and can be described by a graph set motif of C(5). The combination of both interactions generates a two-dimensional network, which lies parallel to the (0 0 1) plane.

In the case of **11b,** there are two symmetry-independent molecules in the asymmetric unit. The most significant difference between the independent molecules is in the orientation of the Cl-atom. Furthermore, each of the two symmetry-independent molecules is disordered over the Cl-$(CH_2)_3$- section of the molecule. Two positions were defined for these atoms in each molecule, except for the Cl-substituted C-atom, which is common to both conformations.

[5]) We expect that in the presence of a better nucleophile a competition with the attack of Cl^- should be possible, which would lead to a mixture of products, but all reactions in the presence of CsI, Bu_4NI and PhSNa, respectively, led to the formation of **11** exclusively.

[6]) The structure of **11c** has also been proven by an X-ray crystal-structure determination. The quality of the crystals and, subsequently, the results of the structure determination were poor, although unambiguous. The results are not reported here, but have been deposited at the CCDC (see footnote 6).

a)



b)

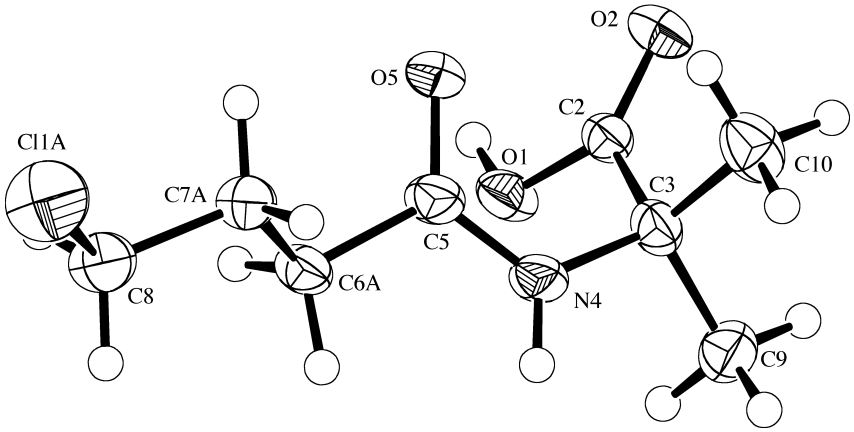
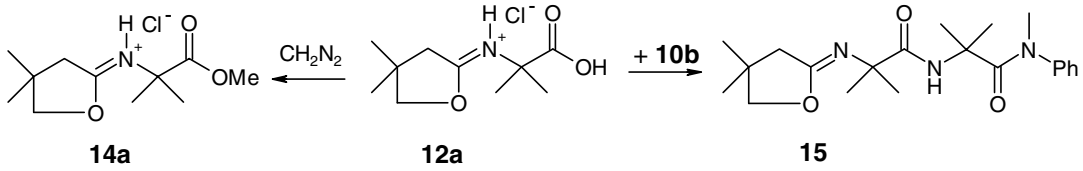


Fig. 2. ORTEP *Plots* [24] *of the molecular structures of a)* **11a** *and b) one of the disordered conformations of one of the two symmetry-independent molecules of* **11b** *(arbitrary numbering of the atoms; 50% probability ellipsoids)*

The major conformation is present in approximately 65% and 80% of molecules A and B, respectively. Except for the orientations of the Cl-atoms, the major conformation of molecule A is almost identical to that of the minor conformation of molecule B and *vice-versa*. The OH group of each molecule in **11b** forms an intermolecular hydrogen bond with the amide O-atom of an adjacent molecule of the same type. These interactions link the molecules into infinite extended chains composed entirely of molecules of type A or entirely of type B. These chains run in the [1 0 1] direction and can be described by a graph set motif of C(7). The amide group of each

molecule forms an intermolecular H-bond with the carbonyl O-atom of the carboxyl group of an adjacent symmetry-independent molecule. These interactions link the molecules into extended ···A···B···A···B··· chains which run in the [0 0 1] direction and can be described by a binary graph set motif of $C_2^2(10)$. The combination of all H-bonding interactions links the molecules into extended two-dimensional networks which lie parallel to the (0 1 0) plane.

In order to isolate the crucial intermediate **12a**, extraction with aq. Na_2CO_3 solution [26] and deprotection by treatment with polyvinylpyridine were attempted, but neither procedure gave satisfying results. Although esterification of **12a** with CH_2N_2 yielded the corresponding crude methyl ester hydrochloride **14a** (*Scheme 5*), the product was also not stable in polar solvents and isomerized partially to the corresponding chloro ester.



14a **12a** **15**

Scheme 5

Finally, the reaction of **12a** with 2*H*-azirin-3-amine **10b** yielded the diamide **15**, which was stable in solution and whose structure was confirmed by X-ray crystallography (*Fig. 3*). This is the first direct proof of the tetrahydrofuran-2-imine structure.

The central amide group (N(4)H) of **15** has a weak intramolecular H-bonding interaction with the imine N-atom (N(7)), which results in a five-membered loop that can be described by a graph set motif [25] of S(5).

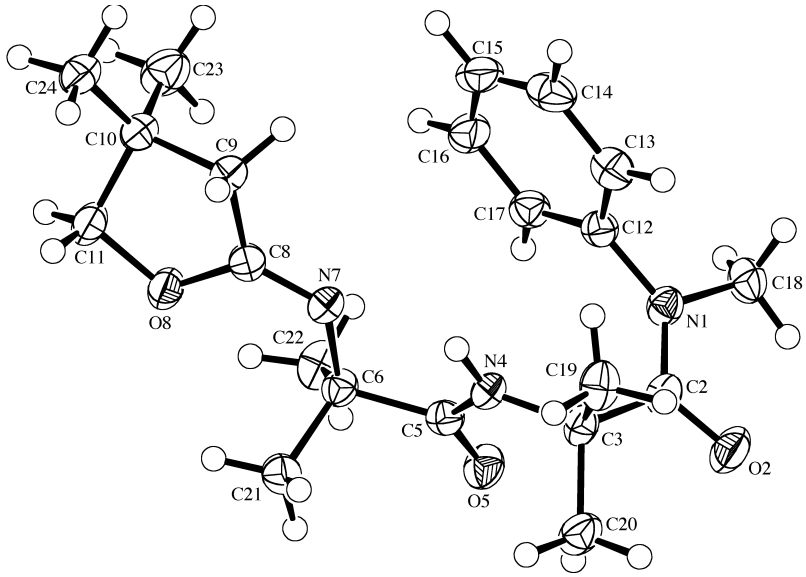
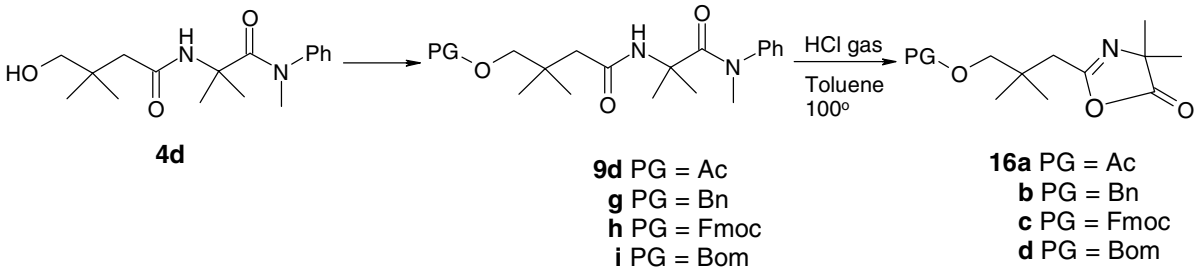


Fig. 3. ORTEP *Plot* [24] *of the molecular structure of* **15** *(arbitrary numbering of the atoms; 50% probability ellipsoids)*

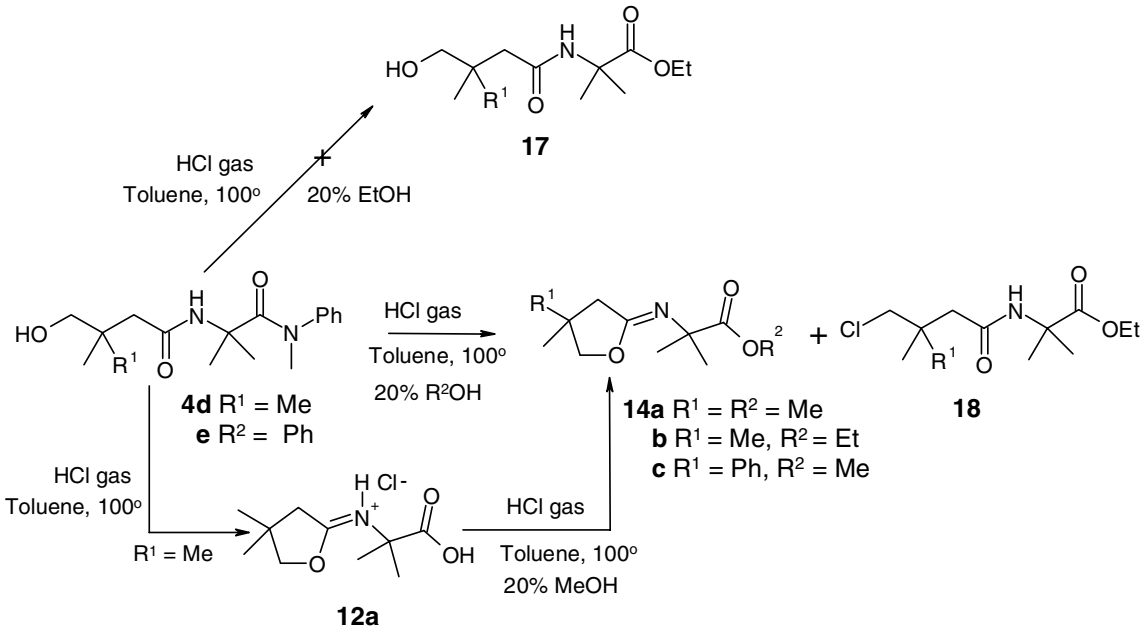
When the hydroxy-protected amide **9d** was subjected to the DAC conditions, the corresponding protected 1,3-oxazol-5(4*H*)-one **16a** (*Scheme 6)* was isolated in good yield, which indicated that an oxazolone, *i.e.* **13** in *Scheme 4,* is most probably the first intermediate from which the imino lactones **12** and the chloro acids **11** are formed. Therefore, we decided to prepare **9g-i** with different protecting groups, which could potentially allow the deprotection and isolation of the oxazolone with a free hydroxy group as a precursor for the cyclization to give **A**.

We planned to prepare **9g-i** analogously to **9d** (*Scheme 2).* The benzyl, (benzyloxy)methyl (Bom) and Fmoc protecting group could be introduced before the oxidative clevage of the double bond and yield the protected acids of type **8,** which could then be reacted with 2*H*-azirin-3-amine **10b** to give the protected diamides **9**. Because of the instability of the protecting group under the oxidation conditions, direct protection of the hydroxy amide **4d** was preferred (*Scheme 6*). Unfortunately, the deprotection failed in all cases.



Scheme 6

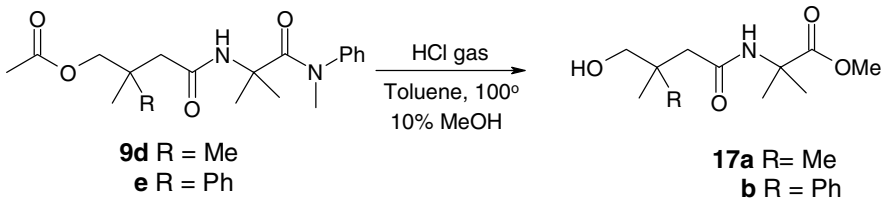
Since the DAC method failed to give cyclic depsipeptides, we attempted to synthesize the hydroxy esters of type **17** from amides **4** and to subject them to the NaH cyclization procedure, described earlier [16][17]. Unexpectedly, treatment of **4d** and **4e** with HCl gas in toluene containing 20% EtOH as an external nucleophile did not yield the desired esters **17,** but gave as the main products the imino lactone esters **14** in moderate yields together with the corresponding ω-chloro esters **18** (*Scheme 7*).



Scheme 7

Further experiments with **4d** in the presence of MeOH showed that the ester could also be formed directly from the imino lactone **12a,** either under DAC conditions or by treatment with CH_2N_2 (*Schemes 5* and *7).*

If instead of the hydroxy amides **4,** the protected alcohols **9d** or **9f** were subjected to the DAC conditions in the presence of MeOH, the unprotected linear esters **17** were formed (*Scheme 8*). We believe that again oxazolones are the intermediates and since the OH group in **9** is protected, it is to be expected that protected oxazolones of type **16** (*Scheme 6*) are the intermediates. Nucleophilic addition of MeOH to the oxazolone, followed by ring opening, leads to the ester group in **17**. The deacetylation could be explained by trans-esterification, *via* formation of AcOMe, which is a common reaction under acidic conditions.

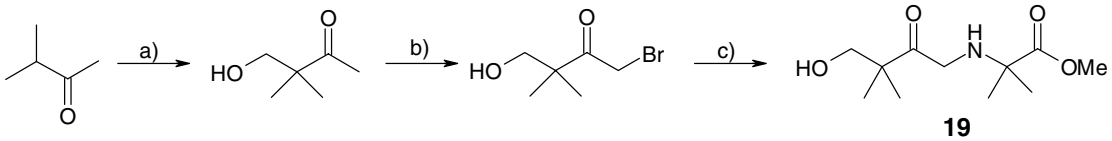


9d R = Me
e R = Ph

17a R= Me
b R = Ph

Scheme 8

The esters **17** were subjected to the conditions of the NaH-catalyzed cyclization, *i.e.* they were treated with NaH in toluene at 80° [16][27], but no cyclic products were obtained. As in previous studies [16][17], the rigidity of the amide bond was suggested as the reason for the failure. Therefore, the aminoketone **19** was synthesized, as depicted in *Scheme 9*, and subjected to the same reaction conditions. Again, no cyclic products could be identified in the mixture.



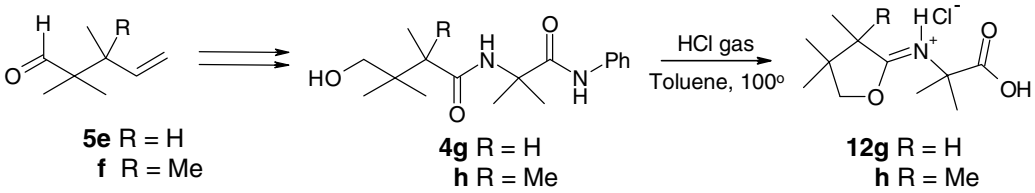
19

a) HCHO, NaOH, 72%; b) Br_2, 88%; c) Ethyl 2-amino-2-methylpropanoate hydrochloride, Et_3N, 39%

Scheme 9

If indeed the formation of the cyclic products **12** and **14** occurs *via* the attack of the OH group at the imminium C-atom of the oxazolone **12** (see *Scheme 4*, path b), α-substitution in the hydroxy diamide **4** might present sufficient steric hindrance in order to direct the nucleophilic attack onto

the ester group (*Scheme 4*, path a). Therefore, the amides **4g** and **4h** were prepared, analogously to *Scheme 2*. Treatment of amides **4g** and **4h** with HCl gas in toluene at 100° (DAC conditions) yielded imino lactones as sole products (*Scheme 10).*



5e R = H
f R = Me

4g R = H
h R = Me

12g R = H
h R = Me

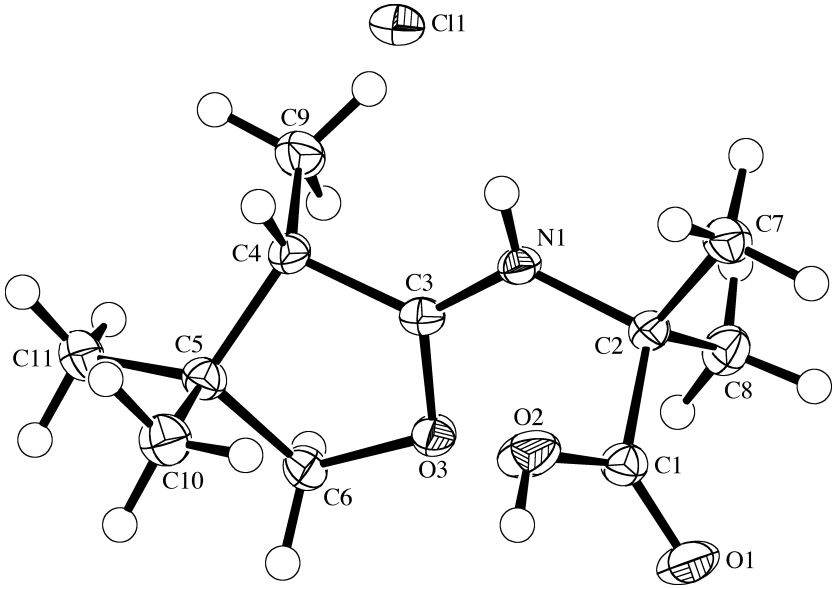
Scheme 10

Unlike their analogues **12a-c,** compounds **12g,h** are stable in solution. The higher substitution of the ring apparently stabilizes it, *i.e.* the *gem*-dimethyl effect (*Thorpe-Ingold* effect [28]) makes the ring opening thermodynamically unfavorable. Thanks to their stability in solution, crystals suitable for an X-ray crystal structure determination could be grown for both hydrochlorides **12g** and **12h** (*Fig*. *4*).

Since the space group of **12g** is centrosymmetric, the compound in the crystal is racemic. The OH group forms a H-bond with a neighboring chloride ion, while the imminium group forms a H-bond with a different chloride ion. Thus, each chloride ion accepts two H-bonds. These interactions link two cations and two anions in a cyclic manner into a tetrameric unit and can be described by a graph set motif [25] of $R_4^2(14)$.

Similar H-bonding interactions occur in **12h,** but this time the interactions link the ions into extended chains, which run parallel to the [1 0 0] direction and can be described by a graph set motif of $C_2^1(7)$.

a)



b)

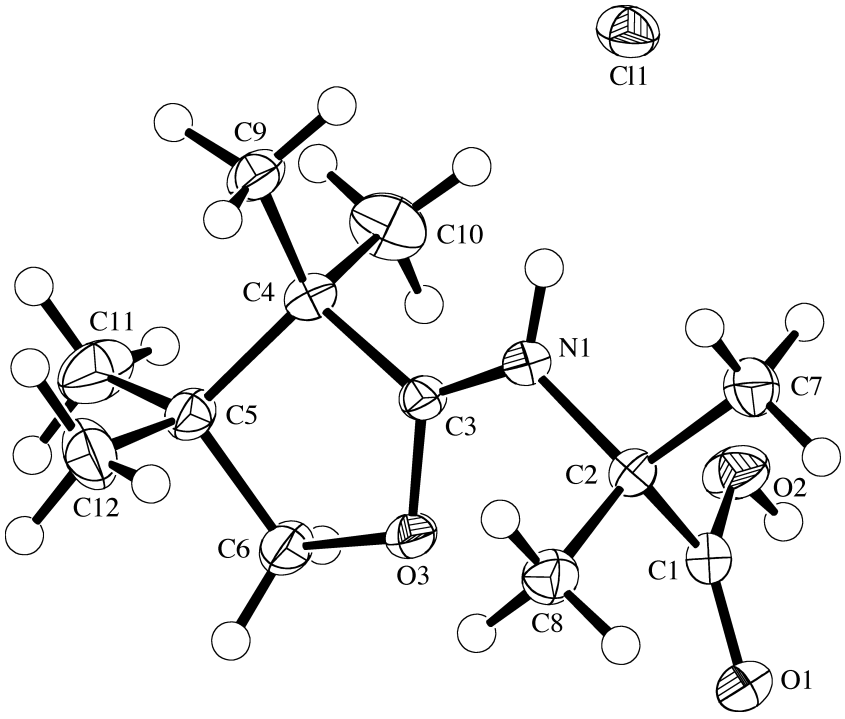


Fig. 4. ORTEP *Plots* [24] *of the molecular structures of a)* **12g** *and b)* **12h** *(arbitrary numbering of the atoms; 50% probability ellipsoids)*

3. Conclusions

When γ-hydroxy diamides **4** were subjected to the DAC reaction conditions, neither the 8-membered nor the 16 membered depsipeptides were formed. Depending on the work-up procedure, either the chlorinated acids **11** or the imino lactone hydrochlorides **12** with a carboxyl group were obtained as the sole products in good yields. Both products are formed *via* the intermediate oxazolones by an attack of the OH group at the iminium C-atom, instead of at the carbonyl group of the oxazolone (*Scheme 4*). This attack leads to the five-membered ring, instead of the desired eight-membered ring. The former are obviously more stable than the latter.

Compounds **12**, with α-H atoms next to the carbonyl group, are unstable in solution and isomerize to the corresponding ω-chloro acids **11**. Increased substitution of the imino lactone stabilizes the five membered ring and prevents isomerization. A few other cyclization methods were also tried, but they all failed to give cyclic depsipeptides.

Experimental Part

1. *General*. See [16].

2. *Starting Materials*. 2,2,*N*,*N*-Tetramethyl-2*H*-azirin-3-amine (**10a**), 2,2,*N*-trimethyl-*N*-phenyl-2*H*-azirin-3-amine (**10b**), and *N*,*N*-dimethyl-1-azaspiro[2.4]hept-1-en-2-amine (**10c**) were prepared according to standard procedures (*cf.* [16] and refs. cited therein). 2,2-Dimethylpent-4-enal (**5a**) was prepared from isobutyraldehyde according to *Noack et al.* [29], 2-phenylpent-4-en-1-ol (**6c**) was obtained from 2-phenylpropanal by following the method of *Iqbal et al.* [30], and 2-methyl-2-phenylpent-4-enal (**5d**) was synthesized from 2-phenylpropanal analogously to **5a**. All spectra were in accordance with literature data [31]. 2,2,3-Trimethylpent-4-enal (**5e)** and 2,2,3,3-tetramethylpent-4-enal (**5f**) were prepared according to *Brannock et al.* [32] from crotyl bromide and 1-bromo-3-methylbut-2-ene, respectively. 1-Bromo-4-hydroxy-3,3-dimethylbutan-2-one (**23)** was synthesized according to *Mihelcic et al.* [33]. All other products used were commercially available.

3. *Preparation of Pent-4-enyl Acetates. General Procedure 1 (GP 1).* To a soln. of the corresponding pent-4-enal **5** (5 mmol) in MeOH (20 ml) at 0^{o}, $NaBH_4$ (760 mg, 20 mmol) was added in small portions within 20 min, then the mixture was allowed to warm to r.t. and was stirred for a total of 1 h. The solvent was evaporated *i.v.* and the residue dissolved in H_2O. Extraction with Et_2O (5 × 30 ml), drying ($MgSO_4$) and evaporation *i.v.* yielded the pent-4-en-1-ols **6**, which were acetylated without further purification. For this purpose, **6** (5 mmol) was dissolved in Et_2O (50 ml) and pyridine (0.81 ml, 10 mmol) was added. The mixture was heated to reflux and a soln. of Ac_2O (0.41 ml, 5.5 mmol) in Et_2O (10 ml) was added dropwise within 20 min. The mixture was stirred under reflux for another 1.5 h, cooled, the salt was filtered off, the org. layer washed with 10% aq. $CuSO_4$ soln. and brine, dried ($MgSO_4$), evaporated *i.v.* and purified by column chromatography (CC, SiO_2) to yield the desired pent-4-enyl acetates **7**.

3.1. *2,2-Dimethylpent-4-enyl Acetate* (**7a**). According to *GP 1* from 2,2-dimethylpent-4-enal (**5a**, 560 mg, 5 mmol), CC (hexane/Et_2O 10:1). Yield: 593 mg, 79% of **7a** as a colorless oil. All spectra were in accordance with literature data [34].

3.2. *2-Phenylpent-4-enyl Acetate* (**7c**). To a soln. of 2-phenylpent-4-en-1-ol (**6c**, 5 mmol, 810 mg) in Et_2O (50 ml), pyridine (0.81 ml, 10 mmol) was added, the mixture was heated to reflux and then a soln. of Ac_2O (0.71 ml, 5.5 mmol) in Et_2O (10ml) was added dropwise over 20 min. The reaction was stirred under reflux for another 1.5 h, cooled, the pyridinium acetate filtered off, the org. layer washed with 10% aq. $CuSO_4$ soln. and brine, dried ($MgSO_4$), evaporated *i.v.* and purified by CC (hexane/Et_2O 15:1) to yield 860 mg (84%) of **7c**. Colorless oil. ^{1}H-NMR: 1.98 (*s*, MeCO); 2.24-2.41 (*m*, CH_2); 2.91-3.06 (*m*, PhC*H*); 4.11-4.26 (*m*, CH_2O); 4.92-5.09 (*m*, C*H*$_2$=CH); 5.62-5.83 (*m*, CH_2=C*H*); 7.12-7.39 (*m*, 5 arom. H). ^{13}C-NMR: 20.8 (*q*, Me); 36.8 (*t*, CH_2); 44.4 (*d*, CH); 67.6 (*t*, CH_2O); 116.6 (*t*, *C*H$_2$=CH); 126.7, 127.4, 128.3 (3*d*, 5 arom. CH), 135.6 (*d*, CH_2=*C*H); 141.3 (*s*, arom. C); 170.8 (*s*, C=O). ESI-MS: 205 (100, $[M + H]^+$).

3.3. *2-Methyl-2-phenylpent-4-enyl Acetate* (**7d**). According to *GP 1* from 2-methyl-2-phenylpent-4-enal (**5d**, 870 mg, 5 mmol), CC (hexane/Et_2O 20:1). Yield: 785 mg (72%) of **7d**. Colorless oil. IR: 3075*s*, 2962v*s*, 2860v*s*, 1745v*s*, 1636*s*, 1482*s*, 1432*s*, 1386*s*, 1334*s*, 1188*s*, 1076*s*, 1029*s*, 912*m*. ^{1}H-NMR: 1.35 (*s*, Me); 2.05 (*s*, MeCO); 2.31-2.59 (*m*, CH_2); 4.13-4.28 (*m*, CH_2O); 4.87-5.11 (*m*, C*H*$_2$=CH); 5.45-5.59 (*m*, CH_2=C*H*); 7.14-7.44 (*m*, 5 arom. H). ^{13}C-NMR: 20.7, 22.5 (2*q*, 2 Me); 41.0 (*s*, C); 43.4 (*t*, CH_2); 71.4 (*t*, CH_2O); 117.8 (*t*, *C*H$_2$=CH); 126.1, 127.7, 128.1 (3*d*, 5

arom. CH); 133.3 (*d*, CH_2=*C*H); 144.3 (*s*, arom. C); 170.9 (*s*, C=O). ESI-MS: 219 (100, [*M* + H]$^+$).

3.4. *2,2,3-Trimethylpent-4-enyl Acetate* (**7e)**. According to *GP 1*, from 2,2,3-trimethylpent-4-enal (**5e,** 5 mmol, 630 mg), CC (hexane/Et_2O 10:1). Yield: 604 mg (71%) of **7e**. Colorless oil. IR: 3077*w*, 2973v*s*, 2879*s*, 1744v*s*, 1637*m*, 1473*m*, 1377*s*, 1036*s*, 914*m*. ^{1}H-NMR: 0.86, 0.90 (2*s*, Me_2C); 0.98 (*d*, *J* = 4.5, Me); 1.98 (*s*, MeCO); 2.11-2,23 (*m*, MeC*H*); 3.36 (*s*, CH_2O); 4.90-5.04 (*m*, C*H*$_2$=CH); 5.74-5.92 (*m*, CH_2=C*H*). ^{13}C-NMR: 14.6, 20.8, 21.6 (3*q*, Me, *Me*$_2$C, *Me*CO); 36.5 (*s*, Me_2*C*), 40.9 (*d*, Me*C*H); 70.4 (*t*, CH_2O); 114.1 (*t*, *C*H_2=CH); 141.5 (*d*, CH_2=*C*H); 171.8 (*s*, C=O). ESI-MS: 193 (100, [*M* + H]$^+$).

3.5. *2,2,3,3-Tetramethylpent-4-enyl Acetate* (**7f**). According to *GP 1*, from 2,2,3,3-tetramethylpent-4-enal (**5f,** 5 mmol, 700 mg), CC (hexane/Et_2O 10:1). Yield: 717 mg (78%) of **7f**. Colorless oil. IR: 3072*m*, 2964v*s*, 2909*s*, 1746v*s*, 1635*m*, 1473*m*, 1414*m*, 1380*s*, 1315*s*, 1040*s*, 913*s*. ^{1}H-NMR: 0.88, 0.99 (2*s*, 2 Me_2C); 2.02 (*s*, MeCO); 3.90 (*s*, CH_2O); 4.89-5.00 (*m*, C*H*$_2$=CH); 5.87-5.96 (*m*, CH_2=C*H*). ^{13}C-NMR: 20.5 (*q*, *Me*$_2$C); 21.0 (q, *Me*CO); 22.6 (*q*, *Me*$_2$C); 38.3, 40.8 (2*s*, 2 Me_2*C*); 70.6 (*t*, CH_2O); 112.0 (*t*, *C*H_2=CH); 145.3 (*d*, CH_2=*C*H); 171.3 (*s*, C=O). ESI-MS: 207 (100, [*M* + H]$^+$).

4. *4-Acetoxybutanoic Acids* **8.** *General Procedure 2 (GP 2)*. To a soln. of pent-4-enyl acetates **7** (5 mmol) in MeCN/CCl_4/H_2O 2:2:3 (70 ml), $NaIO_4$ (2.28 g, 20 mmol) was added under stirring. After 10 min, a catalytic amount of RuO_2.H_2O was added and the mixture stirred vigorously at r.t. for 4-12 h. Filtration of the white residue over celite, washing with CH_2Cl_2, extraction of the collected mother liquor with CH_2Cl_2, drying ($MgSO_4$), evaporation *i.v.* and purification by CC yielded **8** as colorless oils.

4.1. *4-Acetoxy-3,3-dimethylbutanoic Acid* (**8a**). According to *GP 2* from **7a** (5 mmol, 780 mg), 6 h, CC (CH_2Cl_2/MeOH 20:1). Yield: 625mg (73%) of **8a.** Colorless oil. IR: 3284 *s* (br), 2969*s*, 1739v*s*, 1709v*s*, 1475*w*, 1379*s*, 1243*s*, 1041*s*, 926*w*. ^{1}H-NMR: 0.98 (*s*, Me_2C); 1.98 (*s*, MeCO); 2.28 (*s*, CH_2); 3.88 (*s*, CH_2O); 9.83 (br. *s*, COOH). ^{13}C-NMR: 20.6 (*q*, Me); 24.9 (*q*, *Me*$_2$C); 33.5 (*s*, Me_2*C*), 42.8 (*t*, CH_2); 71.6 (*t*, CH_2O); 171.1 (*s*, C=O); 177.7 (*s*, COOH). ESI-MS: 197 (100, [*M* + Na]$^+$).

4.2. *4-Acetoxy-3-phenylbutanoic Acid* (**8c)**. According to *GP 2*, **7c** (5 mmol, 1.020 g), 4 h, CC (CH_2Cl_2/acetone 20:1). Yield: 678 mg (61%) of **8c**. Colorless oil. ^{1}H-NMR: 1.99 (*s*, MeCO);

2.61-2.88 (*m*, CH_2); 3.42-3.58 (*m*, PhC*H*); 4.09-4.36 (*m*, CH_2O); 7.13-7.38 (*m*, 5 arom. H.); 10.63 (br. *s*, COOH). ^{13}C-NMR: 20.6 (*q*, *Me*CO); 37.1 (*t*, CH_2), 40.7 (*d*, CH); 67.3 (*t*, CH_2O); 127.2, 127.5, 128.6 (3*d*, 5 arom. CH); 139.8 (*s*, arom. C); 170.7 (*s*, C=O); 177.3 (*s*, COOH). ESI-MS: 245 (100, $[M + Na]^+$).

4.3. *4-Acetoxy-3-methyl-3-phenylbutanoic Acid* (**8d**). According to *GP 2* from **7d** (5 mmol, 1090 mg), 6 h, CC (CH_2Cl_2/MeOH 20:1). Yield: 861mg (73%) of **8d.** Colorless oil. ^{1}H-NMR: 1.31 (*s*, Me); 2.01 (*s*, MeCO); 2.28-2.36 (*m*, CH_2); 4.18-4.45 (*m*, CH_2O); 7.08-7.38 (*m*, 5 arom. H). ^{13}C-NMR: 20.9 (*q*, *Me*CO); 26.6 (*q*, Me); 31.1 (*s*, Me_2C); 45.7 (*d*, CH); 69.3 (*t*, CH_2O); 127.3, 127.6, 128.9 (3*d*, 5 arom. CH); 141.2 (*s*, arom. C); 171.4 (*s*, C=O); 176.1 (*s*, COOH). ESI-MS: 259 (100, $[M + Na]^+$).

4.4. *4-Acetoxy-2,3,3-trimethylbutanoic Acid* (**8e**). According to *GP 2* from **7e** (5 mmol, 850 mg), 6 h, CC (CH_2Cl_2/MeOH 20:1). Yield: 771mg (82%) of **8e**. Colorless oil. IR: 3466 br. *s*, 2976*s*, 1738v*s*, 1710v*s*, 1467*w*, 1390*s*, 1245*s*, 1041*s*, 925*w*. ^{1}H-NMR: 0.95, 0.99 (2*s*, Me_2C); 1.18 (*d*, *J* = 4.7, *Me*CH); 2.00 (*s*, MeCO); 2.48 (*q*, *J* = 4.7, MeC*H*); 3.89 (*s*, CH_2O); 10.11 (br. *s*, COOH). ^{13}C-NMR: 15.6, 20.6 (2*q*, 2 Me); 21.8, 22.1 (2*q*, *Me*$_2$C); 38.7 (*s*, Me_2C); 45.1 (*d*, CH); 70.8 (*t*, CH_2O); 171.0 (*s*, C=O); 181.3 (*s*, COOH). ESI-MS: 211 (100, $[M + Na]^+$).

4.5. *4-Acetoxy-2,2,3,3-tetramethylbutanoic Acid* (**8f**). According to *GP 2* from **7f** (5 mmol, 920 mg), 4 h, CC (CH_2Cl_2/MeOH 20:1). Yield: 524 mg (52%) of **8f**. IR: 3290*s* (br), 2972*s*, 1743v*s*, 1477*m*, 1377*m*, 1248*s*, 1214*w*, 1040*s*, 1021*w*, 926*w*. ^{1}H-NMR: 0.99, 1.19 (2*s*, 2 Me_2C); 2.03 (*s*, MeCO); 3.99 (*s*, CH_2O); 9.63 (br. *s*, COOH). ^{13}C-NMR: 20.6 (*q*, MeCO); 21.1, 21.4 (2*s*, 2 *Me*$_2$C); 38.3, 46.9 (2*s*, 2 Me_2C); 70.1 (*t*, CH_2O); 171.1 (*s*, C=O); 183.3 (*s*, COOH). CI-MS: 203 (38, $[M + H]^+$), 143 (100, $[M - MeCO]^+$).

5. *Coupling of* **8** *with 2*H*-Azirin-3-amines* **10.** *General Procedure 3 (GP 3).* Acids **8** were taken up in dry THF (20 ml) and the corresponding aminoazirine **10** was added dropwise. The mixture was stirred overnight at r.t., the solvent evaporated *i.v.* and the residue purified by CC to yield acetoxy diamides **9**.

5.1. *3-[1-Methyl-1-(*N,N*-dimethylcarbamoyl)ethylcarbamoyl]-2,2-dimethylpropyl Acetate* (**9a**). According to *GP 3* from **8a** (348 mg, 2 mmol) in dry THF (20 ml) and **10a** (235 mg, 2.1 mmol), CC (CH_2Cl_2/MeOH 30:1). Yield: 509 mg (89%) of **9a**. White powder. M.p. 99.1-99.2°. ^{1}H-NMR: 0.98, 1.52 (2*s*, 2 Me_2C); 2.05 (*s*, MeCO); 2.10 (*s*, CH_2); 3.08 (br. *s*, Me_2N); 3.98 (*s*, CH_2O); 7.12

(*s*, NH). ^{13}C-NMR: 20.9 (*q*, *Me*CO); 24.5, 24.7 (2*q*, 2 *Me*$_2$C); 34.1 (*s*, Me$_2$*C*); 38.2 (*q*, Me$_2$N); 45.5 (*t*, CH$_2$); 56.8 (*s*, Me$_2$*C*); 71.8 (*t*, CH$_2$O); 169.4, 171.2, 173.2 (3*s*, 3 C=O). ESI-MS: 309 (100, [*M* + Na]$^+$]).

5.2. *3-[1-(*N,N-*Dimethylcarbamoyl)cyclopentylcarbamoyl]-2,2-dimethylpropyl Acetate* (**9c**). According to *GP 3* from **8a** (348 mg, 2 mmol) in dry THF (20 ml) and **10c** (290 mg, 2.1 mmol), CC (CH$_2$Cl$_2$/MeOH 20:1). Yield: 549 mg (88%) of **9c**. White powder. M.p. 139.0-140.2°. ^{1}H-NMR: 1.02 (*s*, Me$_2$C); 1.66-1.78, 1.83-1.93 (2*m*, 4 CH$_2$); 2.07 (*s*, MeCO); 2.18-2.26 (*m*, CH$_2$); 2.98 (br. *s*, Me$_2$N); 3.96 (*s*, CH$_2$O); 6.41 (br. *s*, NH). ^{13}C-NMR: 21.0 (*q*, *Me*CO); 22.4 (*t*, CH$_2$); 24.6 (*q*, *Me*$_2$C); 34.3 (*t*, CH$_2$); 35.7 (*s*, Me$_2$*C*); 38.2 (*q*, Me$_2$N); 44.3 (*t*, CH$_2$); 66.8 (*s*, Me$_2$*C*); 71.9 (*t*, CH$_2$O); 169.8, 171.4, 172.5 (3*s*, 3 C=O). CI-MS: 313 (40, [*M* + H]$^+$), 268 (100, [*M* - NMe$_2$]$^+$),

5.3. *3-[1-Methyl-1-(*N-*methyl*-N-*phenylcarbamoyl)ethylcarbamoyl]-2,2-dimethylpropyl Acetate* (**9d**). According to *GP 3* from **8a** (348 mg, 2 mmol) in dry THF (20 ml) and **10b** (365 mg, 2.1 mmol), CC (CH$_2$Cl$_2$/MeOH 40:1). Yield: 584 mg (84%) of **9d**. White powder. M.p. 94.1-95.8°. ^{1}H-NMR: 0.99, 1.48 (2*s*, 2 Me$_2$C); 2.03 (*s*, MeCO); 2.12 (*s*, CH$_2$); 3.26 (*s*, MeN); 3.91 (*s*, CH$_2$O); 6.38 (*s*, NH); 7.21-7.43 (*m*, 5 arom. H). ^{13}C-NMR: 20.9 (*q*, *Me*CO); 24.4, 26.0 (2*q*, 2 *Me*$_2$C); 34.0 (*s*, Me$_2$*C*); 41.5 (*q*, MeN); 46.0 (*t*, CH$_2$); 58.3 (*s*, Me$_2$*C*); 71.7 (*t*, CH$_2$O); 127.9, 128.2, 129.3 (3*d*,5 arom. CH); 144.5 (*s*, arom. C); 169.6, 171.2, 173.4 (3*s*, 3 C=O). ESI-MS: 371 (100, [*M* + Na]$^+$]).

5.4. *3-[1-Methyl-1-(*N-*methyl*-N-*phenylcarbamoyl)ethylcarbamoyl]-2-phenylpropyl Acetate* (**9e**). According to *GP 3* from **8c** (444 mg, 2 mmol) in dry THF (20 ml) and **10b** (365 mg, 2.1 mmol), CC (CH$_2$Cl$_2$/MeOH 50:1). Yield: 689 mg (87%) of **9e**. White powder. M.p. 133.3-134.2°. ^{1}H-NMR: 1.32, 1.38 (2*s*, Me$_2$C); 2.09 (*s*, MeCO); 2.18-2.25, 2.43-2.50 (2*m*, CH$_2$); 3.20-3.26 (*m*, MeN, CH); 3.72-3.77 (*m*, CH$_2$O); 5.97 (*s*, NH); 7.17-7.36 (*m*, 10 arom. H). ^{13}C-NMR: 21.1 (*q*, *Me*CO); 26.1, 26.2 (2*q*, *Me*$_2$C); 40.9 (*t*, CH$_2$); 41.3 (*q*, MeN); 44.5 (*d*, CH); 58.1 (*s*, Me$_2$*C*); 67.0 (*t*, CH$_2$O); 126.9, 127.5, 127.9, 128.6, 129.3 (5*d*, 5 arom. CH); 141.8, 144.4 (2*s*, 2 arom. C); 169.9, 171.0, 173.0 (3*s*, 3 C=O). ESI-MS: 419 (100, [*M* + Na]$^+$).

5.5. *3-[1-Methyl-1-(*N-*methyl*-N-*phenylcarbamoyl)ethylcarbamoyl]-2-methyl-2-phenylpropyl Acetate* (**9f**)**.** According to *GP 3* from **8d** (472 mg, 2 mmol) in dry THF (20 ml) and **10b** (365 mg, 2.1 mmol), CC (CH$_2$Cl$_2$/MeOH 50:1). Yield: 689 mg (84%) of **9f**. White powder. M.p. 135.1-136.6°. ^{1}H-NMR: 1.08, 1.16, 1.36 (3*s*, Me, Me$_2$C); 2.08 (*s*, MeCO); 2.11-2.17 (*m*, CH$_2$); 3.16 (*s*, MeN); 4.21 (*s*, CH$_2$O); 5.64 (*s*, NH); 7.09-7.41 (*m*, 10 arom. H). ^{13}C-NMR: 20.8 (*q*, *Me*CO);

22.4, 26.1, 26.6 (3*q*, Me, *Me*$_2$C); 30.8 (*s*, Me$_2$*C*); 41.1 (*q*, MeN); 46.3 (*t*, CH_2); 57.4 (*s*, Me$_2$*C*); 71.1 (*t*, CH_2O); 126.1, 127.6, 127.9, 128.5, 128.9, 129.3 (6*d*, 10 arom. CH); 143.6, 144.8 (2*s*, 2 arom. C); 168.9, 170.8, 172.9 (3*s*, 3 C=O). CI-MS: 411 (42, $[M + H]^+$), 304 (100, $[M - Me(Ph)N]^+$), 175 (21).

5.6. *3-[1-Methyl-1-(*N-*methyl*-N-*phenylcarbamoyl)ethylcarbamoyl]-2,2-dimethylbutyl Acetate* (**9g**). According to *GP 3* from **8e** (372 mg, 2 mmol) in dry THF (20 ml) and **10b** (365 mg, 2.1 mmol), CC (CH_2Cl_2/MeOH 50:1). Yield: 637 mg (88%) of **9g.** White powder. M.p. 139.6-140.9°. ^{1}H-NMR: 0.99, 1.00 (2*s*, Me$_2$C); 1.05 (*d*, *J* = 3.9, *Me*CH); 1.40, 1.41 (2*s*, Me$_2$C); 2.05-2.12 (*m*, MeCO, CH); 3.19 (*s*, MeN); 3.86 (*q*, CH_2O); 6.66 (*s*, NH); 7.14-7.46 (*m*, 5 arom. H). ^{13}C-NMR: 12.2 (*q*, Me); 20.8 (*q*, *Me*CO); 21.6, 22.4, 24.8, 25.0 (4*q*, 2 *Me*$_2$C); 35.9 (*s*, Me$_2$*C*); 41.4 (*q*, MeN); 46.4 (*d*, CH); 58.5 (*s*, Me$_2$*C*); 71.3 (*t*, CH_2O); 128.0, 128.4, 129.3 (3*d*, 5 arom. CH); 144.1 (*s*, arom. C); 170.9, 172.7, 173.7 (3*s*, 3 C=O). ESI-MS: 385 (100, $[M + Na]^+$).

5.7. *3-[1-Methyl-1-(*N-*methyl*-N-*phenylcarbamoyl)ethylcarbamoyl]-2,2,3-trimethylbutyl Acetate* (**9h**). According to *GP 3* from **8f** (404 mg, 2 mmol) in dry THF (20 ml) and **10b** (365 mg, 2.1 mmol), CC (CH_2Cl_2/MeOH 50:1). Yield: 684 mg (91%) of **9h.** White powder. M.p. 119.9-120.9°. ^{1}H-NMR: 0.93, 1.11, 1.47 (3*s*, 3 Me$_2$C); 2.04 (*s*, MeCO); 3.26 (*s*, MeN); 3.98 (*s*, CH_2O); 7.04 (*s*, NH); 7.18-7.41 (*m*, 5 arom. H). ^{13}C-NMR: 21.0, 21.7, 24.9 (3*q*, 3 *Me*$_2$C); 38.6 (*s*, Me$_2$*C*); 41.7 (*q*, MeN); 47.2, 58.8 (2*s*, 2 Me$_2$*C*); 70.7 (*t*, CH_2O); 128.3, 128.6, 129.5 (3*d*, 5 arom. CH); 144.1 (*s*, arom. C); 171.1, 174.3, 176.9 (3*s*, 3 C=O). ESI-MS: 415 (20, $[M + K]^+$), 399 (100, $[M + Na]^+$), 377 (60, $[M + H]^+$). Anal. calc. for $C_{21}H_{32}N_2O_4$ (376.50): C 66.99, H 8.57, N 7.44; found: C 66.35, H 8.28, N 7.15.

6. *Deprotection of* **9** *to give Hydroxydiamides* **4.** *General Procedure 4 (GP 4).* The amides **9** were treated with 4 equiv. of LiOH in THF/H_2O 2:1 at r.t. for 4-12 h. Evaporation of the solvent *i.v.*, extraction of the residue with CH_2Cl_2, drying ($MgSO_4$), evaporation *i.v.* and washing with Et_2O yielded the hydroxydiamides **4** as white powders, which were used without further purification.

6.1. *4-Hydroxy-3,3-dimethyl*-N-*[1-methyl-1-(*N,N-*dimethylcarbamoyl)ethyl]butanamide* (**4a**). According to *GP 4* from **9a** (858 mg, 3 mmol), 4 h. Yield: 677 mg (93%) of **4a**. White powder. M.p. 138.6-139.9°. ^{1}H-NMR: 0.99, 1.64 (2*s*, Me$_2$C); 2.14 (*s*, CH_2); 3.12 (br. *s*, Me$_2$N); 3.91 (*s*, CH_2O); 7.02 (*s*, NH). ^{13}C-NMR: 24.6, 24.8 (2*q*, 2 *Me*$_2$C); 34.6 (*s*, Me$_2$*C*); 38.8 (*q*, Me$_2$N); 45.4 (*t*,

CH_2); 56.8 (*s*, Me_2C); 71.3 (*t*, CH_2O); 171.4, 173.0 (2*s*, 2 C=O). CI-MS: 244 (32, $[M + H]^+$]), 201 (100, $[M - Me_2N]^+$]).

6.2. *4-Hydroxy*-N-*[1-methyl-1-(*N,N-*dimethylcarbamoyl)ethyl]butanamide* (**4b**). A soln. of sodium 4-hydroxy-butanate (1.0 g, 7.9 mmol) in H_2O (10 ml) was acidified with 3N HCl. Extraction with AcOEt (5 × 30 ml), drying ($MgSO_4$), evaporation of the solvent *i.v.* yielded 520 mg (63%) of 4-hydroxybutanoci acid as a viscous fluid, which was used without further purification. All spectra were in accordance with the data in [35]. 4-Hydroxybutanoic acid (600 mg, 5.77 mmol) was dissolved in dry THF (20 ml) and **10a** (711 mg, 6.35 mmol, 1.1 equiv.) was added dropwise. The mixture was stirred overnight at r.t., the solvent evaporated *i.v.* and the residue purified by CC (CH_2Cl_2/MeOH 10:1). Yield: 1134 mg (90%) of **4b**. White solid. M.p. 124.6-125.3°. ^{1}H-NMR: 1.48 (*s*, Me_2C); 1.73-1.82 (*m*, CH_2); 2.08 (*t*, *J* = 6.2, CH_2); 3.26 (*s*, Me_2N); 3.65 (*t*, *J* = 6.2, CH_2O); 6.38 (*s*, NH); 7.24-7.32 (*m*, 5 arom. H). ^{13}C-NMR: 24.4 (*t*, CH_2); 26.0 (*q*, *Me*$_2$C); 41.5 (*q*, Me_2N); 46.0 (*t*, CH_2); 58.3 (*s*, Me_2C); 71.7 (*t*, CH_2O); 127.9, 128.2, 129.3 (3*d*, 5 arom. CH); 144.5 (*s*, arom. C); 171.2, 173.4 (2*s*, 2 C=O). CI-MS: 279 (85, $[M + H]^+$), 172 (100, $[M - Me_2N]^+$).

6.3. *4-Hydroxy-3,3-dimethyl*-N-*[1-(*N,N-*dimethylcarbamoyl)cyclopentyl]butanamide* (**4c**). According to *GP 4* from **9c** (936 mg, 3 mmol), 6 h. Yield: 738 mg (91%) of **4c**. White powder. M.p. 138.4-139.9°. ^{1}H-NMR: 0.99 (*s*, Me_2C); 1.62-1.76, 1.84-2.02 (2*m*, 4 CH_2); 2.21-2.39 (*m*, CH_2); 3.03 (br. *s*, Me_2N); 3.38 (*s*, CH_2O); 6.61 (br. *s*, NH). ^{13}C-NMR: 24.4 (*t*, CH_2); 25.2 (*q*, *Me*$_2$C); 35.7 (*s*, Me_2C); 37.3 (*t*, CH_2); 37.9 (*q*, Me_2N); 46.4 (*t*, CH_2); 66.6 (*s*, C); 71.9 (*t*, CH_2O); 172.2, 172.7 (2*s*, 2 C=O). ESI-MS: 309 (10, $[M + K]^+$), 293 (100, $[M + Na]^+$).

6.4. *4-Hydroxy-3,3-dimethyl*-N-*[1-methyl-1-(*N-*methyl*-N-*phenylcarbamoyl) ethyl]butanamide* (**4d**). According to *GP 4*, from **9d** (1044 mg, 3 mmol), 6 h. Yield: 845 mg (92%) of **4d**. White powder. M.p. 138.4-139.9°. ^{1}H-NMR: 0.92, 1.44 (2*s*, 2 Me_2C); 2.13 (*s*, CH_2); 3.22 (*s*, MeN); 3.91 (*s*, CH_2O); 6.32 (*s*, NH); 7.16-7.41 (*m*, 5 arom. H). ^{13}C-NMR: 25.2, 26.0 (2*q*, 2 *Me*$_2$C); 35.6 (*s*, Me_2C); 41.3 (*q*, MeN); 47.2 (*t*, CH_2); 58.2 (*s*, Me_2C); 71.4 (*t*, CH_2O); 127.9, 128.2, 129.2 (3*d*, 5 arom. CH); 144.3 (*s*, arom. C); 171.6, 173.1 (2*s*, 2 C=O). ESI-MS: 345 (20, $[M + K]^+$), 329 (100, $[M + Na]^+$). Anal. calc. for $C_{17}H_{26}N_2O_3$ (306.41): C 66.64, H 8.55, N 9.14; found: C 66.36, H 8.49, N 8.97.

6.5. *4-Hydroxy*-N-*[1-methyl-1-(*N-*methyl*-N-*phenylcarbamoyl)ethyl]-3-phenyl butanamide* (**4e**). According to *GP 4*, from **9e** (1188 mg, 3 mmol), 8 h. Yield: 934 mg (88%) of **4e**. White powder. M.p. 129.0-129.9°. ^{1}H-NMR: 1.28, 1.35 (2*s*, Me_2C); 2.11-2.21, 2.34-2.46 (2*m*, CH_2); 3.17 (br. *s*, MeN, CH); 3.64-3.79 (*m*, CH_2O); 5.96 (*s*, NH); 7.10-7.41 (*m*, 10 arom. H). ^{13}C-NMR: 26.1, 26.2 (2*q*, *Me*$_2$C); 40.9 (*q*, MeN); 41.2 (*t*, CH_2); 44.5 (*d*, CH); 58.2 (*s*, Me_2*C*); 67.1 (*t*, CH_2O); 126.8, 127.5, 127.9, 128.6, 129.3 (5*d*, 10 arom. CH); 141.7, 144.4 (2*s*, 2 arom. C); 171.1, 173.0 (2*s*, 2 C=O). CI-MS (i-butane): 355 (100, $[M + H]^+$).

6.6. *4-Hydroxy*-N-*[1-methyl-1-(*N-*methyl*-N-*phenylcarbamoyl)ethyl]-3-methyl-3-phenylbutanamide* (**4f**). According to *GP 4* from **9f** (820 mg, 2 mmol), 12 h. Yield: 587 mg (90%) of **4f**. White powder. M.p. 121.9-123.3°. ^{1}H-NMR: 1.22, 1.23, 1.24 (3*s*, Me, *Me*$_2$C); 2.11-2.19, 2.31-2.38 (2*m*, CH_2); 3.15 (*s*, MeN); 3.51-3.59, 3.83-3.89 (2*m*, CH_2O); 5.84 (*s*, NH); 7.11-7.43 (*m*, 10 arom. H). ^{13}C-NMR: 23.6, 26.1, 26.2 (3*q*, Me, *Me*$_2$C); 41.4 (*q*, Me_2N); 42.7 (*s*, Me_2*C*); 47.4 (*t*, CH_2); 58.1 (*s*, Me_2*C*); 70.6 (*t*, CH_2O); 126.1, 126.5, 127.8, 128.5, 129.3 (5*d*, 10 arom. CH); 144.5, 145.5 (2*s*, 2 arom. C); 170.9, 173.0 (2*s*, 2 C=O). CI-MS (i-butane): 327 (80, $[M + H]^+$), 221 (100, $[M - Ph(Me)N]^+$).

6.7. *4-Hydroxy-2,3,3-trimethyl*-N-*[1-methyl-1-(*N-*methyl*-N-*phenylcarbamoyl) ethyl]butanamide* (**4g**). According to *GP 4* from **9g** (724 mg, 2 mmol), 4 h. Yield: 576 mg (90%) of **4g**. White powder. M.p. 124.2-126.3°. ^{1}H-NMR: 1.00 (*s*, Me_2C); 1.09 (*d*, *J* = 4.6, *Me*CH); 1.40, 1.42 (2*s*, Me_2C); 2.08 (*q*, *J* = 4.6, CH); 3.18 (*s*, MeN); 3.51-3.59 (*m*, CH_2O); 6.96 (*s*, NH); 7.12-7.42 (*m*, 5 arom. H). ^{13}C-NMR: 12.7 (*q*, Me); 23.4, 24.2, 25.0 (3*q*, 3 *Me*$_2$C); 37.6 (*s*, Me_2*C*); 41.7 (*q*, MeN); 49.9 (*d*, CH); 58.9 (*s*, Me_2*C*); 69.3 (*t*, CH_2O); 128.4, 128.6, 129.5 (3*d*, 5 arom. CH); 143.9 (*s*, arom. C); 173.8, 175.6 (2*s*, 2 C=O). ESI-MS: 343 (100, $[M + Na]^+$).

6.8. *4-Hydroxy-2,2,3,3-tetramethyl*-N-*[1-methyl-1-(*N-*methyl*-N-*phenylcarbamoyl)ethyl]-butanamide* (**4h**). According to *GP 4*, from **9h** (752 mg, 2 mmol), 4 h. Yield: 608 mg (91%) of **9h**. White powder. M.p. 129.9-131.3°. ^{1}H-NMR: 0.88, 1.15, 1.46 (3*s*, 3 Me_2C); 3.29 (*s*, MeN); 3.44 (*s*, CH_2O); 6.48 (*s*, NH); 7.23-7.42 (*m*, 5 arom. H). ^{13}C-NMR: 21.5, 21.9, 24.6 (3*q*, 3 *Me*$_2$C); 39.6 (*s*, Me_2*C*); 41.6 (*q*, MeN); 47.6, 58.9 (2*s*, 2 Me_2*C*); 70.7 (*t*, CH_2O); 128.2, 128.4, 129.4 (3*d*, 5 arom. CH); 143.9 (*s*, arom. C); 173.9, 177.8 (2*s*, 2 C=O). ESI-MS: 357 (100, $[M + Na]^+$).

7. *Attempted Direct Amide Cyclizations of Amides* **4.** *General Procedure 5 (GP 5)*. A suspension of **4** (0.5 mmol) in dry toluene (50 ml) was heated to 100° and HCl gas was bubbled through the

suspension for 4-6 min. Then, the mixture was allowed to cool to r.t. while bubbling N_2 through it (*ca*. 20 min). The solvent was evaporated, the white residue was washed with CH_2Cl_2 (3×15 ml) and dried in *h.v*. to yield imino lactone hydrochlorides **12** as white powders.

General Procedure 6 (GP 6). A suspension of **4** was treated as in *GP 5*. The solvent was evaporated, and the oily residue was purified by CC to yield the ω-chloro acids **11**.

7.1. *2-[(4,4-Dimethyltetrahydrofuran-2-yliden)amino]-2-methylpropanoic Acid Hydrochloride* (**12a**). According to *GP 5* from **4d** (153 mg, 0.5 mmol). Yield: 101 mg (84%). M.p. 158.3-159.1°. IR: 3431*w*, 2938*s*, 2804*s*, 1735v*s*, 1678v*s*, 1529*s*, 1414*m*, 1319*m*, 1194*s*, 1166*s*, 1003*m*, 946*m*, 754*m*. ^{1}H-NMR ((D$_6$)DMSO): 1.15, 1.56 (2*s*, 2 Me$_2$C); 3.13 (*s*, CH$_2$); 4.56 (*s*, CH$_2$O); 13.2 (br. *s*, COOH). ^{13}C-NMR ((D$_6$)DMSO): 23.5, 24.1 (2*q*, 2 *Me*$_2$C); 38.0, 60.1 (*s*, Me$_2$*C*); 88.0 (*t*, CH$_2$O); 162.0 (C=N); 180.2 (*s*, C=O). CI-MS: 200 (100, [*M* - Cl]$^+$).

7.2. *2-[(3,4,4-Trimethyltetrahydrofuran-2-yliden)amino]-2-methylpropanoic Acid Hydrochloride* (**12g**). According to *GP 5* from **4g** (160 mg, 0. 5mmol). Yield: 78 mg (73%). M.p. 152.4-153.6°. IR: 3386*w*, 2986*s*, 2776*s*, 1739v*s*, 1671v*s*, 1514*m*, 1478*s*, 1240*m*, 1178*s*, 1165*s*, 997*s*, 773*m*. ^{1}H-NMR ((D$_6$)DMSO): 1.08 (*d*, *J* = 4.9, Me); 1.21, 1.48 (2*s*, 2 Me$_2$C); 2.18 (*q*, *J* = 4.9, CH); 4.42 (*s*, CH$_2$O); 10.0 (br. *s*, COOH). ^{13}C-NMR ((D$_6$)DMSO): 12.0 (*q*, Me); 21.1, 22.2 (2*q*, 2 *Me*$_2$C); 36.5 (*s*, Me$_2$*C*); 46.1 (*d*, CH); 58.2 (*s*, Me$_2$*C*); 87.2 (*t*, CH$_2$O); 163.1 (C=N); 178.0 (*s*, C=O). CI-MS (i-butane): 214 (100, [*M* - Cl]$^+$), 108 (25). Anal. calc. for $C_{11}H_{20}NO_3Cl$ (249.74): C 52.90, H 8.07, N 5.61; found C 50.55, H 7.87, N 5.25.

7.3. *2-[(3,3,4,4-Tetramethyltetrahydrofuran-2-yliden)amino]-2-methylpropanoic Acid Hydrochloride* (**12h).** According to *GP 5* from **4h** (167 mg, 0.5 mmol). Yield: 79 mg (78%), M.p. 157.0-157.6°. IR: 3390*w*, 3024*s*, 2938*s*, 2778*s*, 1738v*s*, 1669v*s*, 1476*s*, 1400*s*, 1313*m*, 1178*s*, 998*m*, 880*m*, 772*m*. ^{1}H-NMR ((D$_6$)DMSO): 0.97, 1.26, 1.56 (3*s*, 3 Me$_2$C); 4.58 (*s*, CH$_2$O); 12.9 (br. *s*, COOH). ^{13}C-NMR ((D$_6$)DMSO): 21.6, 22.5, 26.1 (3*q*, 3 *Me*$_2$C); 42.8, 46.6, 60.7 (3*s*, 3 Me$_2$*C*); 86.8 (*t*, CH$_2$O); 168.1 (C=N); 183.2 (*s*, C=O). ESI-MS: 228 (100, [*M* + Na]$^+$).

7.4. *2-(4-Chloro-3,3-dimethylbutanoylamino)-2-methylpropanoic Acid* (**11a**). According to *GP 6* from **4a** (122 mg, 0.5 mmol) or from **4d** (153 mg, 0.5 mmol), CC (CH_2Cl_2/acetone 10:1). Yield: 57 mg (48%) of **11a** from **4a** and 62 mg (52%) from **4d**. White powder. M.p. 116.1-117.3°. IR: 3356v*s*, 2981*s*, 2605*m*, 1717v*s*, 1620v*s*, 1548v*s*, 1473*s*, 1393*s*, 1294*m*, 1221*s*, 1158*s*, 1023*m*, 895*m*, 791*s*. ^{1}H-NMR ((D$_6$)DMSO): 1.00, 1.31 (2*s*, 2 Me$_2$C); 2.09 (*s*, CH$_2$); 3.59 (*s*, CH$_2$Cl); 7.12 (br. *s*, NH); 12.9 (br. *s*, COOH). ^{13}C-NMR ((D$_6$)DMSO): 24.9, 25.8 (2*q*, 2 *Me*$_2$C); 36.6 (*s*, Me$_2$*C*);

44.9 (*t*, CH_2); 55.3 (*t*, CH_2Cl); 60.3 (*s*, Me_2C); 172.1, 181.1 (2*s*, 2 C=O). ESI-MS: 260 (32, $[M(^{37}Cl) + Na]^+$), 258 (100, $[M(^{35}Cl) + Na]^+$).

7.5. *2-(4-Chlorobutanoylamino)-2-methylpropanoic Acid* (**11b**). According to *GP 6* from **4b** (140 mg, 0.5 mmol), CC (CH_2Cl_2/acetone 10:1). Yield: 62 mg (66%) of **11b**. White solid. M.p. 111.9-113.1°. IR: 3318v*s*, 2988*s*, 1721v*s*, 1623*s*, 156*s*, 1467*s*, 1399*m*, 1230*m*, 1166*s*, 1050*w*, 945*w*, 787*m*. ^{1}H-NMR: 1.57 (*s*, Me_2C); 2.07-2.13 (*m*, CH_2); 2.37 (*t*, *J* = 6.1, CH_2); 3.61 (*t*, *J* = 6.1, CH_2Cl); 7.29 (br. *s*, NH). ^{13}C-NMR : 24.7 (*q*, *Me*$_2$C); 33.9 (*t*, CH_2); 44.4 (*t*, CH); 55.6 (*t*, CH_2Cl); 59.6 (*s*, Me_2C); 171.8, 176.6 (2*s*, 2 C=O). CI-MS: 210 (10, $[M(^{37}Cl) + NH_4]^+$), 208 (25, $[M(^{35}Cl) + NH_4]^+$), 172 (100, $[M - Cl]^+$).

7.6. *1-[(4-Chloro-3,3-dimethylbutyl-1-oxo)amino]cyclopentanecarboxylic Acid* (**11c**). According to *GP 6* from **4c** (135 mg, 0.5 mmol), CC (CH_2Cl_2:acetone 10:1). Yield: 69 mg (53%) of **11c**. White powder. M.p. 113.2-114.7°. ^{1}H-NMR: 1.02, 1.09 (2*s*, Me_2C); 1.71-1.76, 1.94-2.02 (2*m*, 4 CH_2); 3.22 (*m*, CH_2); 3.63 (*m*, CH_2Cl); 7.47 (br. *s*, NH). ^{13}C-NMR: 24.8 (*t*, CH_2); 25.3 (*q*, *Me*$_2$C); 36.3 (*q*, Me_2C); 37.5, 44.7 (2*t*, 2 CH_2); 55.0 (*t*, CH_2Cl); 66.1 (*s*, Me_2C); 171.7, 176.4 (2*s*, 2 C=O). CI-MS: 264 (28, $[M(^{37}Cl) + H]^+$), 262 (72, $[M(^{35}Cl) + H]^+$), 226 (100, $[M - Cl]^+$).

7.7 *2-(4-Chloro-3-phenylbutanoylamino)-2-methylpropanoic Acid* (**11d**). According to *GP 6* from **4e** (184 mg, 0.5 mmol), CC (CH_2Cl_2/acetone 20:1). Yield: 51 mg (43%) of **11d**. White powder. M.p. 119.6-121.8° (decomp). IR: 3320v*s*, 2928*s*, 1722v*s*, 1626v*s*, 1606*s*, 1557*s*, 1496*s*, 1442*s*, 1315*s*, 1260*m*, 1170*s*, 1079*m*, 752*s*, 696*s*. ^{1}H-NMR: 1.36, 1.39 (2*s*, Me_2C); 2.53-2.60, 2.70-2.78 (*m*, CH_2); 3.48-3.52 (*m*, PhC*H*); 3.85-3.91 (*m*, CH_2Cl); 7.24-7.32 (*m*, 5 arom. H); 7.45 (br. *s*, NH); 12.3 (br. *s*, COOH). ^{13}C-NMR: 24.8, 25.3 (2*q*, 2 *Me*$_2$C); 40.2 (*t*, CH_2); 45.3 (*d*, CH); 55.3 (*t*, CH_2Cl); 59.6 (*s*, Me_2C); 127.6, 128.7, 129.0 (3*d*, 5 arom. CH); 142.3 (*s*, arom. C); 171.1, 179.1 (2*s*, 2 C=O). CI-MS: 286 (15, $[M(^{37}Cl) + H]^+$), 284 (39, $[M(^{35}Cl) + H]^+$), 248 (100, $[M - Cl]^+$).

8. *Synthesis of dipeptide esters. General Procedure 7 (GP 7).* A suspension of **4** (0.5 mmol) in a mixture of dry toluene (50 ml) and alcohol (5 ml) was heated to reflux and HCl gas was bubbled through the suspension for 6 min. Then, the mixture was allowed to cool to r.t. while bubbling N_2 through it (*ca*. 20 min). The solvent was evaporated, and the oily residue was purified by CC to yield the products as colorless oils.

General Procedure 8 (GP 8). To solid **12a** (117 mg, 0.5 mmol), a 0.5 M soln. of CH_2N_2 in Et_2O (1 ml, 0.5 mmol) was added dropwise at 0^o. After the disappearance of the yellow color, another 1 ml of CH_2N_2 was added, the mixture allowed to warm up to r.t., stirred for 15 min, filtered, and the solvent evaporated *i.v.* The white solid **14a** was used without further purification.

8.1. *Methyl 2-[(4,4-Dimethyltetrahydrofuran-2-yliden)amino]-2-methylpropanoate* (**14a**). Accordig to *GP 7* from **4d** (153 mg, 0.5 mmol), 5 ml of MeOH, CC (CH_2Cl_2/acetone 20:1). Yield: 50 mg (43%) of **14a**. White solid. M.p. 88.6-89.8°. IR: 2961*s*, 2876*m*, 1736v*s*, 1706v*s*, 1567*s*, 1360*m*, 1271*s*, 1143*s*, 101*m*, 919*m*, 731*s*. ^{1}H-NMR ((D$_6$)DMSO): 1.05, 1.28 (2*s*, 2 Me$_2$C); 2.24 (*s*, CH_2); 3.56 (*s*, MeO); 3.83 (*s*, CH_2O). ^{13}C-NMR ((D$_6$)DMSO): 23.6, 25.8 (2*q*, *Me*$_2$C); 36.6 (*s*, Me$_2$*C*); 42.4 (*t*, CH_2); 50.1 (*q*, MeO); 58.9 (*s*, Me$_2$*C*); 80.3 (*t*, CH_2O); 162.2 (*s*, C=N); 175.3 (*s*, C=O). CI-MS: 231 (100, $[M + NH_4]^+$).

An experiment according to *GP 8* yielded 113 mg (98%) of **14a** as a white solid.

8.2. *Ethyl 2-[(4,4-Dimethyltetrahydrofuran-2-yliden)amino]-2-methylpropanoate* (**14b).** According to *GP 7* from **4d** (153 mg, 0.5 mmol), 5 ml of EtOH, after CC (CH_2Cl_2/acetone 20:1). Yield: 49 mg (43%) of **14b** and 51 mg of *ethyl 2-(4-chloro-3,3-dimethylbutanoylamino)-2-methylpropanoate* **18b** (38%) as colorless oils.

14b: IR: 2965v*s*, 2893*s*, 1714v*s*, 1697v*s*, 1468*s*, 1380*s*, 1273*s*, 1166*s*, 1035*m*, 911*m*, 731*s*. ^{1}H-NMR: 1.11 (*s*, Me$_2$C); 1.21 (*t*, *J* = 7.1, *Me*CH$_2$); 1.43 (*s*, Me$_2$C); 2.33 (*s*, CH_2); 3.82 (*s*, CH_2O); 4.18 (*q*, *J* = 7.1, MeC*H*$_2$). ^{13}C-NMR: 14.3 (*q*, Me); 25.1, 26.6 (2*q*, *Me*$_2$C); 37.1 (*s*, Me$_2$*C*); 44.5 (*t*, CH_2); 60.4 (*t*, Me*C*H$_2$); 60.5 (*s*, Me$_2$*C*); 81.9 (*t*, CH_2O); 163.7 (*s*, C=N); 176.5 (*s*, C=O). ESI-MS: 477 (15, $[2M + Na]^+$), 250 (100, $[M + Na]^+$), 228 (12, $[M + H]^+$).

18b: ^{1}H-NMR: 1.05 (*s*, Me$_2$C); 1.16 (*t*, *J* = 7.2, *Me*CH$_2$); 1.27 (*s*, Me$_2$C); 2.24 (*s*, CH_2); 3.81 (*s*, CH_2Cl); 4.02 (*q*, *J* = 7.2, MeC*H*$_2$); 6.02 (br. *s*, NH). ^{13}C-NMR: 14.2 (*q*, Me); 24.7, 25.8 (2*q*, 2 *Me*$_2$C); 35.8 (*s*, Me$_2$*C*); 38.4 (*t*, CH_2); 54.9 (*t*, CH_2O); 61.3 (*t*, Me*C*H$_2$); 65.6 (*s*, Me$_2$*C*); 170.4, 172.6 (2*s*, 2 C=O). ESI-MS: 288 (31), 286 (100, $[M + Na]^+$).

8.3. *Methyl 2-Methyl-2-[(4-methyl-4-phenyltetrahydrofuran-2-yliden)amino]propanoate* (**14c**). According to *GP 7* from **4f** (168 mg, 0.5 mmol), 5 ml of MeOH, CC (CH_2Cl_2/acetone 25:1). Yield: 77 mg (56%) of **14c**. Colorless oil. ^{1}H-NMR: 1.45, 1.46, 1.49 (3*s*, Me, Me$_2$C) ; 2.73-2.79, 2.97-3.02 2 (2*m*, CH_2); 3.68 (*s*, MeO); 4.31 (*s*, CH_2O); 7.16-7.36 (*m*, 5 arom. H). ^{13}C-NMR: 26.1, 26.7, 27.1 (3*q*, Me, *Me*$_2$C); 43.0 (*t*, CH_2); 44.6 (*s*, Me$_2$*C*); 51.3 (*q*, MeO); 60.1 (*s*, Me$_2$*C*); 80.9 (*t*,

CH_2O); 127.3, 126.8, 128.7 (3*d*, 5 arom. CH); 144.5 (*s*, arom. C); 163.0 (*s*, C=N); 176.7 (*s*, C=O). CI-MS: 276 (100, $[M + H]^+$), 108 (22).

8.4. *Ethyl 1-[(4,4-Dimethyltetrahydrofuran-2-yliden)amino]cyclopentanecarboxylate* (**14d**). According to *GP 7* from **4c** (135 mg, 0.5 mmol), 5 ml of EtOH, CC (CH_2Cl_2/acetone 20:1). Yield: 71 mg (28%) of **14d** and 45 mg (31%) of *ethyl 1-(4-chloro-3,3-dimethylbutanoylamino)cyclopentanecarboxylate* (**18d**) as colorless oils.

14d: ^{1}H-NMR: 1.12 (*s*, Me_2C); 1.21 (*t*, *J* = 7.0, *Me*CH_2); 1.81-1.94 (*m*, 4 CH_2); 2.41 (*s*, CH_2); 3.89 (*s*, CH_2O); 4.14 (*q*, *J* = 7.0, MeC*H*$_2$). ^{13}C-NMR: 14.3 (*q*, Me); 25.1 (*q*, *Me*$_2$C); 37.3, 37.6, 38.4, 39.1 (4*t*, 4 CH_2); 44.2 (*s*, Me_2*C*); 44.9, 47.1 (2*t*, 2 CH_2); 60.6 (*s*, Me_2*C*); 82.2 (*t*, CH_2O); 162.4 (*s*, C=N); 174.9 (*s*, C=O). CI-MS: 254 (100, $[M + H]^+$), 200 (18, $[M - Et]^+$), 158 (36).

18d: ^{1}H-NMR: 1.09 (*s*, Me_2C); 1.20 (*t*, *J* = 6.9, *Me*CH_2); 1.74-1.82, 1.84-1.94 (2*m*, 4 CH_2, Me_2C); 2.16 (*s*, CH_2); 3.56 (*s*, CH_2O); 4.16 (*q*, *J* = 6.9, MeC*H*$_2$); 6.02 (br. *s*, NH). ^{13}C-NMR: 14.2 (*q*, Me); 24.7, 25.8 (2*q*, 2 *Me*$_2$C); 35.8 (*s*, Me_2*C*); 37.4, 37.7, 38.4, 39.1 (4*t*, 4 CH_2); 44.2 (*t*, CH_2); 54.9 (*t*, CH_2O); 61.3 (*t*, Me*C*H_2); 65.6 (*s*, Me_2*C*); 170.4, 172.6 (2*s*, 2 C=O). CI-MS: 292 (34, $[M(^{37}Cl) + H]^+$), 290 (100, $[M(^{35}Cl) + H]^+$), 254 (28).

8.5. *Methyl 2-(4-Hydroxy-3,3-dimethylbutanoylamino)-2-methylpropanoate* (**17a**). According to *GP 7* from **9d** (174 mg, 0.5 mmol), 5 ml of MeOH, CC (CH_2Cl_2/acetone 20:1). Yield: 56 mg (48%) of **17a**. Colorless oil. ^{1}H-NMR: 0.98, 1.43 (2*s*, 2 Me_2C); 2.11 (*s*, CH_2); 3.29 (*s*, CH_2O); 3.78 (*s*, MeO); 6.25 (*s*, NH). ^{13}C-NMR: 24.6, 25.2 (2*q*, 2 *Me*$_2$C); 35.7 (*s*, Me_2*C*); 46.9 (*t*, CH_2); 52.5 (*q*, MeO); 56.4 (*s*, Me_2*C*); 71.2 (*t*, CH_2O); 171.9, 174.9 (2*s*, 2 C=O). ESI-MS: 254 (100, $[M + Na]^+$).

8.6. *Methyl 2-(4-Hydroxy-3-methyl-3-phenylbutyrylamino)-2-methylpropanoate* (**17b**). According to *GP G* from **9f** (205 mg, 0.5 mmol) with 5 ml MeOH, CC (CH2Cl2/acetone 20:1). Yield 57 mg (38%) of **17b**. Colorless oil. ^{1}H-NMR: 1.38 (*s*, Me_2C); 1.39 (*s*, Me); 2.47-2.51, 2.66-3.70 (2*m*, CH_2); 3.65-3.69, 3.89-3.92 (2*m*, CH_2O); 3.68 (*s*, MeO); 6.25 (*s*, NH); 7.19-7.42 (*m*, 5 arom. H). ^{13}C-NMR: 23.3, 24.5, 24.6 (3*q*, 3 Me); 43.0 (*t*, CH_2); 46.5 (*s*, C); 52.3 (*q*, MeO); 56.1 (*s*, *C*); 70.3 (*t*, CH_2O); 126.0, 126.4, 128.4 (3*d*, 5 arom. CH); 145.4 (*s*, arom. C); 171.2, 174.7 (2*s*, 2 C=O). CI-MS (i-butane): 294 (100, $[M + H]^+$).

9. *Protection of Hydroxy Amide* **4d**. 9.1. *4-Benzyloxy-3,3-dimethyl*-N-*[1-methyl-1-(*N-*methyl*-N-*phenylcarbamoyl)ethyl]butanamide* (**9g**). To a soln. of **4d** (1 mmol, 306 mg) in dry THF (20 ml),

NaH (44 mg, 1.1 mmol, 60% suspension in mineral oil) was added at 0°. After 1 h at r.t., benzylbromide (171 mg, 1 mmol) was added and the mixture heated to reflux for 3 h. Washing with brine, extraction with Et_2O, drying ($MgSO_4$) and evaporation *i.v.* yielded a colorless oil, which was purified by CC (CH_2Cl_2/acetone 40:1). Yield: 329 mg (73%) of **9g**. Colorless oil. ^{1}H-NMR: 0.99, 1.36 (2*s*, 2 Me_2C); 2.18 (*s*, CH_2); 3.12 (*s*, CH_2O); 3.22 (*s*, MeN); 4.43 (*s*, PhCH_2); 5.91 (br. *s*, NH); 7.12-7.43 (*m*, 10 arom. H). ^{13}C-NMR: 25.4, 26.7 (2*q*, 2 *Me*$_2$C); 34.8 (*s*, Me_2C); 41.3 (*q*, MeN); 46.3 (*t*, CH_2); 57.7 (*s*, Me_2C); 73.1 (*t*, CH_2O); 78.5 (*t*, PhCH_2); 127.4, 127.6, 127.7, 127.8, 128.3, 129.2 (6*d*, 10 arom. CH); 138.4, 145.0 (2*s*, 2 arom. C); 170.6, 173.2 (2*s*, 2 C=O). CI-MS (i-butane): 397 (100, $[M + H]^+$).

9.2. *{2,2-Dimethyl-3-[1-methyl-1-(*N-*methyl*-N-*phenylcarbamoyl)ethylcarbamoyl] propyl}[(9*H*-fluoren-9-yl)methyl] Carbonate* (**9h**). To a soln. of **4d** (306 mg, 1 mmol) in CH_2Cl_2 (20 ml), pyridine (3 ml) and FmocCl (284 mg, 1.1 mmol) were added. The mixture was stirred at r.t. for 3 h, diluted with CH_2Cl_2 (30 ml), washed with a 10% $CuSO_4$ soln. and brine, the org. fractions were dried ($MgSO_4$) and evaporated *i.v.* and purified by CC (CH_2Cl_2/acetone 30:1). Yiled: 450 mg (88%) of **9h**. White powder. M.p. 108.9-110.6°. IR: 3320v*s*, 2966*s*, 1745v*s*, 1678v*s*, 1650v*s*, 1599*s*, 1532*s*, 1441*s*, 1386*s*, 1316*m*, 1154*m*, 964*m*, 909*s*, 758*m*. ^{1}H-NMR: 0.99, 1.39 (2*s*, 2 Me_2C); 1.86 (*s*, CH_2); 3.19 (*s*, MeN); 3.92 (*s*, CH_2O); 1.15 (*t*, *J* = 5.8, CH_2CH); 4.36 (*d*, *J* = 5.8, CH_2CH); 6.12 (*s*, NH); 7.09-7.32, 7.50-7.80 (2*m*, 13 arom. H). ^{13}C-NMR: 24.5, 25.5 (2*q*, 2 *Me*$_2$C); 34.2 (*s*, Me_2C); 41.3 (*q*, MeN); 45.3 (*t*, CH_2); 58.0 (*s*, Me_2C); 69.7 (*t*, CH_2O); 75.1 (*t*, CH_2CH); 119.9 (*d*, CH); 125.0, 127.0, 127.7, 127.8, 127.9, 129.1 (6*d*, 13 arom. CH); 141.2, 143.3, 144.5 (3*s*, 5 arom. C); 155.2 (*s*, NC(O)O); 169.4, 173.1 (2*s*, 2 C=O). ESI-MS: 551 (100, $[M + Na]^+$).

9.3. *4-(Benzyloxy)methoxy-3,3-dimethyl*-N-*[1-methyl-1-(*N-*methyl*-N-*phenylcarbamoyl)-ethyl]butanamide* (**9i**). To a soln. of **4d** (306 mg, 1 mmol) in CH_2Cl_2 (20 ml) was added (i-Pr)$_2$NEt (142 mg, 1.1 mmol) and benzyloxymethylchloride (BomCl, 156 mg, 1 mmol). The mixture was stirred at r.t. for 12 h, diluted with CH_2Cl_2 (30 ml), washed with NH_4Cl soln. and brine, dried ($MgSO_4$), evaporated *i.v.* and purified by CC (CH_2Cl_2/acetone 40:1). Yield: 375 mg (88%) **9i**. Colorless oil. ^{1}H-NMR: 0.99, 1.42 (2*s*, 2 Me_2C); 1.84 (*s*, CH_2); 3.22 (*s*, MeN); 3.32 (*s*, CH_2); 4.51, 4.68 (2*s*, CH_2); 5.94 (br. *s*, NH); 7.08-7.42 (*m*, 10 arom. H). ^{13}C-NMR: 25.0, 26.3 (2*q*, 2 *Me*$_2$C); 34.5 (*s*, Me_2C); 41.2 (*q*, MeN); 45.9 (*t*, CH_2); 57.8 (*s*, Me_2C); 69.3, 76.2, 94.8 (3*t*, 3

CH_2); 127.6, 127.7, 127.8, 128.3, 129.0, 129.2 (6*d*, 10 arom. CH); 137.6, 144.6 (2*s*, 2 arom. C); 170.2, 173.1 (2*s*, 2 C=O). CI-MS: 427 (16, $[M + H]^+$), 320 (100, $[M - Ph(Me)N]^+$), 108 (16).

10. *Synthesis of 1,3-Oxazol-5(4*H*)-ones*. 10.1. *3-(4,4-Dimethyl-1,3-oxazol-5(4*H*)-on-2-yl)-2,2-dimethylpropyl Acetate* (**16a**)**.** According to *GP 6* from **9d** (153 mg, 0.5 mmol), 4 min HCl gas, CC (CH_2Cl_2/acetone 40:1). Yield: 123 mg (51%) of **16a**. White solid. M.p. 99.5-101.7°. Recovered starting material: 33 mg (21%). IR: 3385*m*, 2976*s*, 2937*s*, 1820v*s*, 1739v*s*, 1672v*s*, 1525*m*, 1474*s*, 1379*s*, 1240v*s*, 1072*s*, 1041*s*, 966*s*, 897*m*. ^{1}H-NMR: 1.05, 1.36 (2*s*, 2 Me_2C); 2.04 (*s*, MeCO); 2.42 (*s*, CH_2); 3.92 (*s*, CH_2O), 7.21-7.34 (*m*, 5 arom. H). ^{13}C-NMR: 20.8 (*q*, *Me*CO); 24.4, 24.6 (2*q*, 2 *Me*$_2$C); 34.3 (*s*, Me_2C); 38.0 (*t*, CH_2); 65.3 (*s*, Me_2C); 71.6 (*t*, CH_2O); 161.9 (*s*, C=N); 170.9, 181.4 (2*s*, 2 C=O). ESI-MS: 541 (100, $[2(M + H_2O) + Na]^+$), 371 (25), 282 (70, $[M + H_2O + Na]^+$).

10.2. *2-(3-Benzyloxy-2,2-dimethylpropyl)-4,4-dimethyl-1,3-oxazol-5(4*H*)-one* (**16b**). According to *GP 6*, from **9g** (198 mg, 0.5 mmol), 4 min HCl gas, CC (CH_2Cl_2/acetone 50:1). Yield: 49 mg (34%) of **16b**. White powder. M.p. 104.2-106.0°. Recovered starting material: 124 mg (31%). IR: 2951*s*, 1894*s*, 2565*w*,1822v*s*, 1723v*s*, 1612v*s*, 1534v*s*, 1458*s*, 1265*s*, 1101*s*, 1058*m*, 1040*m*, 911*m*. ^{1}H-NMR: 1.01, 1.38 (2*s*, 2 Me_2C); 2.48 (*s*, CH_2); 3.14 (*s*, CH_2O); 4.56 (*s*, PhCH_2); 7.21-7.34 (*m*, 5 arom. H). ^{13}C-NMR: 24.5, 24.9 (2*q*, 2 *Me*$_2$C); 35.4 (*s*, Me_2C); 38.3 (*t*, CH_2); 65.2 (*s*, Me_2C); 73.3 (*t*, CH_2O); 78.6 (*t*, PhCH_2); 127.5, 128.1, 128.3 (3*d*, 5 arom. CH); 138.5 (*s*, arom. C); 162.5 (*s*, C=N); 182.1 (*s*, C=O). CI-MS (i-butane): 290 (18, $[M + H]^+$), 200 (100, $[M - Bn]^+$).

10.3. *[3-(4,4-Dimethyl-1,3-oxazol-5(4*H*)-on-2-yl)-2,2-dimethylpropyl][(9*H*-fluoren-9-yl)methyl] Carbonate* (**16c**). According to *GP 6* from **9h** (169 mg, 0.33 mmol), 4 min HCl gas, CC (CH_2Cl_2/acetone 80:1). Yield: 64 mg (46%) of **16c**. White powder. M.p. 93.8-95.2°. Recovered starting material: 66 mg (39%). IR: 3320*s*, 2966*s*, 1821v*s*, 1745v*s*, 1678v*s*, 1650v*s*, 1599*s*, 1532*s*, 1441*s*, 1386*m*, 1316*m*, 1156*m*, 909*s*. ^{1}H-NMR: 1.01, 1.34 (2*s*, 2 Me_2C); 2.32 (*s*, CH_2); 3.87 (*s*, CH_2O); 4.12 (*t*, *J* = 6.0, CH_2CH); 4.38 (*d*, *J* = 6.0, CH_2CH); 7.18-7.37, 7.53-7.81 (2*m*, 8 arom. H). ^{13}C-NMR: 24.3, 24.8 (2*q*, 2 *Me*$_2$C); 34.5 (*s*, Me_2C); 37.9, 46.7 (2*t*, 2 CH_2); 65.1 (*s*, Me_2C); 65.9 (*t*, CH_2O); 69.8 (*t*, CH_2CH); 119.9 (*d*, CH); 125.0, 126.8, 127.1, 127.7 (4*d*, 8 arom. CH); 141.2, 143.3 (2*s*, 2 arom. C); 155.0 (*s*, NC(O)O); 161.6 (*s*, C=N); 181.1 (*s*, C=O). CI-MS: 422 (16, $[M + H]^+$), 200 (100, $[M - Fmoc]^+$), 179 (44).

10.4. *2-[3-(Benzyloxy)methoxy-2,2-dimethylpropyl]-4,4-dimethyl-1,3-oxazol-5(4*H*)-one (***16d**). According to *GP 6* from **9i** (143 mg, 0.33 mmol), 5 min HCl gas, CC (CH_2Cl_2/acetone 60:1). Yield: 42 mg (36%). White solid. M.p. 104.1-105.8°. Recovered starting material: 52 mg (35%). ^{1}H-NMR: 0.97, 1.36 (2*s*, 2 Me_2C); 2.42, 3.36, 4.59, 4.73 (4*s*, 4 CH_2); 7.14-7.43 (*m*, 5 arom. H). ^{13}C-NMR: 24.4, 24.7 (2*q*, 2 *Me*$_2$C); 34.9 (*s*, Me$_2$*C*); 45.5 (*t*, CH_2); 56.8 (*s*, Me$_2$*C*); 69.3, 76.1, 94.8 (3*t*, 3 CH_2); 127.7, 128.3, 129.5 (3*d*, 5 arom. CH); 137.6 (*s*, arom. C); 162.4 (*s*, C=N); 172.6 (*s*, C=O). CI-MS (i-butane): 320 (100, $[M + H]^+$).

10.5. *2,2-Dimethyl-3-(4-oxo-3-oxa-1-azaspiro[4.4]non-1-en-2-yl)propyl Acetate* (**16e**). According to *GP 6* from **9c** (156 mg, 0.5 mmol), 5 min HCl gas, CC (CH_2Cl_2/acetone 30:1). Yield: 45 mg (34%) of **16e**. White solid. M.p. 101.1-103.1°. Recovered starting material: 33 mg (21%). IR: 3385*w*, 2976*s*, 2937*s*, 1820v*s*, 1739v*s*, 1672v*s*, 1474*m*, 1379*s*, 1240*s*, 1072*s*, 1041*s*, 966*m*. ^{1}H-NMR: 1.01 (*s*, Me$_2$C); 1.73-2.04 (*m*, MeCO, 4 CH_2); 2.42 (*s*, CH_2); 3.90 (*s*, CH_2O). ^{13}C-NMR: 20.8 (*q*, *Me*CO); 24.5 (*q*, *Me*$_2$C); 25.8 (*t*, 2 CH_2); 34.3 (*s*, Me$_2$*C*); 38.0, 38.2 (2*t*, 3 CH_2); 71.6 (*t*, CH_2O); 73.9 (*s*, spiro-C); 161.8 (*s*, C=N); 170.9, 182.1 (2*s*, 2 C=O). ESI-MS: 593 (100, $[2M + H_2O + Na]^+$), 324 (58, $[M + H_2O + K]^+$), 308 (64, $[M + H_2O + Na]^+$), 286 (90, $[M + H_2O + H]^+$).

11. *2-[(4,4-Dimethyltetrahydrofuran-2-yliden)amino]-2-methyl*-N-*[1-methyl-1-(*N-*methyl*-N-*phenylcarbamoyl)ethyl]propanamide* (**15**). To solid **12a** (100 mg, 0.42 mmol) a soln. of **10b** (110 mg, 3 mmol, 1.5 equiv.) in CH_2Cl_2 (5 ml) was added under vigorous stirring. The solvent was immediately removed *i.v.* and the suspension left at r.t. overnight. CC (CH_2Cl_2/acetone 20:1) yielded 102 mg (64%) of **15**. White powder. M.p. 142.1-143.3°. IR: 3364v*s*, 2976*s*, 2937*s*, 1708v*s*, 1666v*s*, 1645v*s*, 1493*s*, 1380*s*, 1223*m*, 1111*m*, 1014*s*, 781*m*, 710*s*. ^{1}H-NMR: 1.08, 1.42, 1.50 (3*s*, 3 Me$_2$C); 2.26 (*s*, CH_2); 3.21 (*s*, MeN); 3.89 (*s*, CH_2O); 7.06-7.29 (*m*, 5 arom. H); 8.07 (br. *s*, NH). ^{13}C-NMR: 23.8, 24.9, 26.1 (3*q*, 3 *Me*$_2$C); 36.5 (*s*, Me$_2$*C*); 41.0 (*q*, MeN); 45.2 (*t*, CH_2); 57.3, 60.6 (2*q*, 2 Me$_2$*C*); 81.5 (*t*, CH_2O); 127.3, 128.1, 129.4 (3*d*, 5 arom. CH); 144.8 (*s*, arom. C); 161.5 (*s*, C=N); 173.6, 176.3 (2*s*, 2 C=O). ESI-MS: 369 (100, $[M + Na]^+$).

12. *Methyl 2-(4-Hydroxy-3,3-dimethyl-2-oxobutylamino)-2-methylpropanoate* (**19**). To a soln. of 1-bromo-4-hydroxy-3,3-dimethylbutan-2-one (390 mg, 2 mmol) in Et_3N (5 ml), methyl 1-amino-2-methylpropanoate hydrochloride (456 mg, 3 mmol) was added. The mixture was heated under

reflux overnight, cooled, diluted with CH_2Cl_2 (150 ml) and washed with a 10% $CuSO_4$ soln. and brine. Drying ($MgSO_4$), evaporation of the solvent and CC (CH_2Cl_2/acetone 30:1) yielded 195 mg (42%) of **19.** Yellow oil. IR: 2973*m*, 2884*m*, 1725v*s*, 1660v*s*, 1528*m*, 1471*s*, 1364*s*, 1192*s*, 1046*m*. ^{1}H-NMR: 1.12, 1.46 (2*s*, 2 Me_2C); 3.50, 3.54 (2*s*, 2 CH_2); 3.71 (*s*, MeO); 6.74 (br. *s*, NH). ^{13}C-NMR: 21.1, 25.1 (2*q*, 2 *Me*$_2$C); 48.4 (*s*, Me$_2$*C*); 49.9 (*t*, CH_2); 51.9 (*q*, MeO); 58.2 (*s*, Me$_2$*C*); 69.4 (*t*, CH_2O); 176.4, 212.6 (2*s*, 2 C=O). CI-MS (i-butane): 232 (70, $[M + H]^+$), 146 (100), 128 (40).

13. *X-ray Crystal-Structure Determination of* **11a, 11b, 12g, 12h** *and* **15** (*Table* and *Figs. 2-4*)[6]. All measurements were made on a *Nonius KappaCCD* area-detector diffractometer [36] using graphite-monochromated MoK_α radiation (λ 0.71073 Å) and an *Oxford Cryosystems Cryostream 700* cooler. The data collection and refinement parameters are given in the *Table* and views of the molecules are shown in *Figs. 2-4*. Data reduction was performed with *HKL Denzo* and *Scalepack* [37]. The intensities were corrected for *Lorenz* and polarization effects, and in the cases of **11a, 12g** and **12h**, an absorption correction based on the multi-scan method [38] was applied. Each structure was solved by direct methods using SIR92 [39], which revealed the positions of all non-H atoms. The non-H atoms were refined anisotropically.

In the case of **11b,** there are two independent molecules in the asymmetric unit. The atomic coordinates of the two molecules were tested carefully for a relationship from a higher symmetry space group using the program *PLATON* [40] but none could be found. Each molecule is disordered over two conformations. Two positions were defined for each atom of the Cl-$(CH_2)_3$-section of each molecule, except for the Cl-substituted C-atom, which is common to both conformations. Bond length restraints were applied to all bonds involving disordered atoms so as to maintain reasonable geometry. The best results were obtained with relative site occupation factors of 0.65:0.35 and 0.80:0.20 for the disordered components of molecules A and B, respectively.

[6] CCDC- 286035 - 286040 contain supplementary crystallographic data for this paper. These data can be obtained free of charge form the *Cambridge Crystallographic Data Centre, via* http://www.ccdc.cam.ac.uk/data_request/cif

The hydroxy and ammonium H-atoms in **12g** and **12h**, as well as the amide H-atom in **15** and the amide and hydroxy H-atoms in **11a** and **11b** were placed in the positions indicated by difference electron density maps and their positions were allowed to refine together with individual isotropic displacement parameters. All remaining H-atoms in all structures were placed in geometrically calculated positions and each was assigned a fixed isotropic displacement parameter with a value equal to $1.2U_{eq}$ of its parent atom ($1.5U_{eq}$ for the Me groups). The refinement of each structure was carried out on F^2 using full-matrix least-squares procedures, which minimized the function $\Sigma w(F_o^2 - F_c^2)^2$. Corrections for secondary extinction were applied, except in the cases of **11a** and **11b**. Neutral atom scattering factors for non-H atoms were taken form [41] and the scattering factors for H-atoms were taken from [42]. Anomalous dispersion effects were included in F_c [43]; the values for f' and f'' were those of [44]. The values of the mass attenuation coefficients are those of [45]. All calculations were performed using the *SHELXL97* program [46]

Table 2. *Crystallographic Data of Compounds* **11a, 11b, 12g, 12h** and **15**

	11a	**11b**
Crystallized from	toluene/CH_2Cl_2/MeCN/acetone	xylene/AcOEt/MeOH
Empirical formula	$C_{10}H_{18}ClNO_3$	$C_8H_{14}ClNO_3$
Formula weight [g mol^{-1}]	235.71	207.66
Crystal color, habit	colorless, prism	colorless, plate
Crystal dimensions [mm]	$0.07 \times 0.17 \times 0.25$	$0.02 \times 0.15 \times 0.20$
Temp. [K]	160(1)	160(1)
Crystal system	monoclinic	triclinic
Space group	$P2_1/c$	$P\bar{1}$
Z	4	4
Reflections for cell determination	18016	4764
2θ range for cell determination [°]	4–60	4–55
Unit cell parameters a [Å]	5.8846(1)	9.5502(2)
b [Å]	10.5564(2)	10.3588(2)
c [Å]	19.0140(4)	11.3586(3)
α [°]	90	92.417(1)
β [°]	91.887(1)	90.584(1)
γ [°]	90	109.313(1)
V [Å^3]	1180.51(4)	1059.16(4)
D_X [g cm^{-3}]	1.326	1.302
μ(MoK_α) [mm^{-1}]	0.312	0.338
Scan type	ϕ and ω	ϕ and ω
2θ(max) [°	60	55
Transmission factors (min; max)	0.887; 0.979	-
Total reflections measured	32539	26265
Symmetry independent reflections	3448	4824
Reflections with $I > 2\sigma(I)$	2459	3464
Reflections used in refinement	3448	4822
Parameters refined; restraints	148; 0	309; 10
R [on F; $I > 2\sigma(I)$ reflections]	0.0443	0.0667
wR [on F^2; all indept. reflections]	0.1158	0.2011
Weighting parameters [a; b][a])	0.0546; 0.3536	0.0996; 0.8346
Goodness of fit	1.046	1.069
Secondary extinction coefficient	-	-
Final Δ_{max}/σ	0.001	0.001
$\Delta\rho$ (max; min) [e Å^{-3}]	0.26; -0.32	0.92; -0.89

a) $w^{-1} = \sigma^2(F_o^2) + (aP)^2 + bP]$ where $P = (F_o^2 + 2F_c^2)/3$

12g	**12h**	**15**
CH_2Cl_2/acetone/*i*-PrOH	CH_2Cl_2/*i*-PrOH/acetone	CH_2Cl_2/Et_2O/hexane
$C_{11}H_{20}ClNO_3$	$C_{12}H_{22}ClNO_3$	$C_{21}H_{31}N_3O_3$
249.74	263.76	373.49
colorless, prism	colorless, prism	colorless, tablet
$0.13 \times 0.20 \times 0.25$	$0.18 \times 0.20 \times 0.25$	$0.12 \times 0.15 \times 0.30$
160(1)	160(1)	160(1)
triclinic	monoclinic	monoclinic
$P\bar{1}$	$P2_1/n$	$P2_1/n$
2	4	4
13668	49886	4258
4−55	4−60	4−52
8.1623(3)	7.0504(1)	10.1674(3)
8.8802(2)	15.0693(2)	19.4044(7)
9.0067(3)	13.0955(2)	11.5235(4)
86.145(2)	90	90
88.338(2)	90.7171(8)	112.515(2)
79.602(2)	90	90
640.56(4)	1391.22(3)	2100.2(1)
1.295	1.259	1.181
0.291	0.272	0.0794
ϕ and ω	ϕ and ω	ω
55	60	52
0.855; 0.968	0.864; 0.957	-
15813	37833	37791
2932	4054	4135
2535	3375	3006
2931	4052	4134
159; 0	169; 0	256; 0
0.0330	0.0370	0.0472
0.0833	0.0960	0.1132
0.0355; 0.2522	0.033; 0.7281	0.0406; 0.6032
1.055	1.055	1.048
0.019(5)	0.009(2)	0.015(2)
0.001	0.001	0.001
0.30; -0.25	0.28; -0.23	0.18; -0.19

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REFERENCES

[1] C. E. Ballard, H. Yu, B. Wang, *Curr. Med. Chem.* **2002**, *9*, 471.

[2] J. S. Davies, *J. Peptide Sci*. **2003**, *9,* 471.

[3] T. G. Back, *Tetrahedron* **1997**, *33*, 3041.

[4] A. Yurek-George, F. Habens, M. Brimmell, G Packham, A. Ganesan, *J. Am. Chem. Soc.* **2004,** *126*, 1030.

[5] C. Palomo, M. Oiarbide, J. Garcia, A. Gonzalez, R. Razos, J. Ordiozola, P. Banuelos, M. Tello, A. Linden, *J. Org. Chem.* **2004**, *69*, 4126.

[6] F. Sarabia, S. Chammaa, F. Lopez-Herrera, *Tetrahedron Lett.* **2002**, *43*, 2961

[7] W. L. Duax, J. F. Griffin, D. A. Langs, G. D. Smith, *Biopolymers*, **1996**, *40*, 141.

[8] P. Vongvilai, M. Isaka, P. Kittakoop, P. Srikitikulchai, P. Kongsaeree, S. Prabpai, Y. Thebtaranonth, *Helv. Chim. Acta* **2004**, *87*, 2066.

[9] A. B. Mauger, *Top. Antibiol. Chem***. 1980**, *5*, 223.

[10] D. Obrecht, H. Heimgartner, *Tetrahedron Lett.* **1983,** *24*, 1921.

[11] D. Obrecht, H. Heimgartner, *Helv. Chim. Acta* **1987,** *70*, 329.

[12] D. Obrecht, H. Heimgartner, *Helv. Chim. Acta* **1984,** *67*, 526.

[13] J. E. F. Magirius, Ph.D. Thesis, University of Zurich, 1995.

[14] K. Koch, A. Linden, H. Heimgartner, *Tetrahedron* **2001**, *57*, 2311.

[15] P. Köttgen, planned Ph.D. Thesis, University of Zurich.

[16] B. Iliev, A. Linden, H. Heimgartner, *Helv. Chim. Acta* **2003**, *86*, 3215.

[17] B. Iliev, A. Linden, H. Heimgartner, *Tetrahedron*, submitted.

[18] P. Wipf, H. Heimgartner, *Helv. Chim. Acta* **1990,** *73*, 13.

[19] R. Miller, W. Theis, G. Heilig, S. Kirchmeyer, *J. Org. Chem.* **1991**, *56*, 1453.

[20] B. Travis, R. Narayan, B. Borhan, *J. Am. Chem. Soc.* **2002,** *124*, 3824.

[21] J. M. Schomaker, B. R. Travis, B. Borhan, *Org. Lett.* **2003**, *5*, 3089.

[22] D. Obrecht, H. Heimgartner, *Helv. Chim. Acta* **1990,** *73,* 221.

[23] H. Heimgartner, *Angew. Chem., Int. Ed.* **1991,** *30,* 238.

[24] C. K. Johnson, 'ORTEP II', Report ORNL-5138, Oak Ridge National Laboratory, Oak Ridge, Tennessee, 1976.

[25] J. Bernstein, R. E. Davis, L. Shimoni, N.-L. Chang, *Angew. Chem., Int. Ed.* **1995,** *34,* 1555.

[26] T. Joseph, J. Tam, M. Kitadani, Y. L. Chow, *Can. J. Chem.* **1976**, *54*, 3517.

[27] S. Richard, G. Prie, A. Guignard, J. Thibonet, J. Luc Parrain, A. Duchene, M. Abarbri, *Helv. Chim. Acta* **2003,** *86,* 726.

[28] R. M. Beesley, C. K Ingold, J. F. Thorpe, *J. Chem. Soc*. **1915**, *105*, 1080.

[29] M. Noack, R. Goettlich, *Eur. J. Org. Chem*. **2002**, 3171.

[30] J. Iqbal, R. Srivastava, *Tetrahedron* **1991**, *47*, 3155.

[31] S. Murahashi, Y. Makabe, K. Kunita, *J. Org. Chem.* **1988**, *53*, 4489.

[32] K. Brannock, R. Burpitt, *J. Am. Chem. Soc.* **1961**, *83*, 3576.

[33] J. Mihelcic, K. Moeller, *J. Am. Chem. Soc* **2003**, *125*, 36.

[34] E. Lee, C. Yoon, T. Lee, S. Kim, T. Ha, Y. Sung, S. Park, S. Lee, *J. Am. Chem. Soc.* **1998,** *120,* 7469.

[35] J. P. Gouesnard, *Bull. Soc. Chim. Fr*. **1989**; 88.

[36] R. Hooft, *KappaCCD Collect Software,* Nonius BV, Delft, The Netherlands, 1999.

[37] Z. Otwinowski, W. Minor, in 'Methods in Enzymology', Vol. 276, 'Macromolecular Crystallography', part A, Eds. C. W. Carter Jr., R. M. Sweet, Academic Press, New York, 1997, p. 307.

[38] R.H. Blessing, *Acta Crystallogr., Sect A* **1995**, *51*, 33.

[39] A. Altomare, G. Cascarano, C. Giacovazzo, A. Guagliardi, M. C. Burla, G. Polidori, M. Camalli, SIR92, *J. Appl. Crystallogr*. **1994**, *27*, 435.

[40] A. L. Spek, PLATON, *J. Appl. Crystallogr.* **2003**, *36*, 7.

[41] E. N. Maslen, A. G. Fox, M. A. O'Keefe, in 'International Tables for Crystallography', Ed. A. J. C. Wilson, Kluwer Academic Publishers, Dordrecht, 1992, Vol. C, Table 6.1.1.1, p. 477.

[42] D. C. Creagh, W. J. McAuley, in 'International Tables for Crystallography', Ed. A. J. C. Wilson, Kluwer Academic Publishers, Dordrecht, 1992, Vol. C, Table 4.2.6.8, p. 219.

[43] D. C. Creagh, J. H. Hubbell, in 'International Tables for Crystallography', Ed. A. J. C. Wilson, Kluwer Academic Publishers, Dordrecht, 1992, Vol. C, Table 4.2.4.3, p. 200.

[44] R. F. Steward, E. R. Davidson, W. T. Simpson, *J. Chem. Phys.* **1965**, *42*, 3175.

[45] J. A. Ibers, W. C. Hamilton, *Acta Crystallogr*. **1964,** *17,* 781.

[46] G. M. Sheldrick, SHELXL97, Program for the Refinement of Crystal Structures, University of Göttingen, Germany, 1997.

Chapter 4

Transformation of 5-Hydroxy- into 5-Chloropentanoylamino Derivatives under 'Direct Amide Cyclization' Conditions [1])

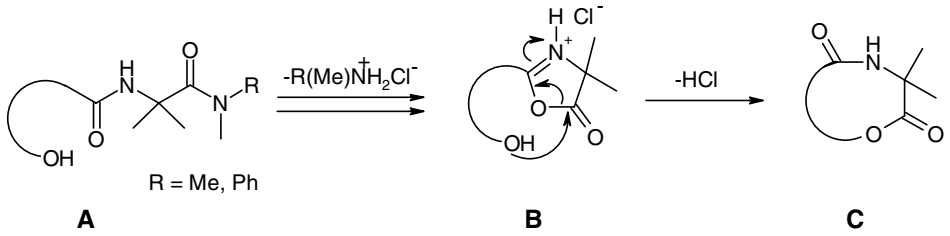
The application of the 'direct amide cyclization' conditions on the δ-hydroxy acid containing linear diamide **11** is described (*Scheme 3).* Instead of the cyclization to the expected 9-membered cyclodepsipeptide, only the chloro acid **12** was obtained**.** Its formation could be explained by consecutive formation of the 1,3-oxazol-5(4*H*)-one **16** and the 6-membered imino lactone **17** as intermediates (*Scheme 4).* The spontaneous isomerization of the latter gave **12** in a good yield.

[1]) B. Iliev. S. Verma, A. Linden, H. Heimgartner, *Helv. Chim. Acta,* submitted.

1. Introduction

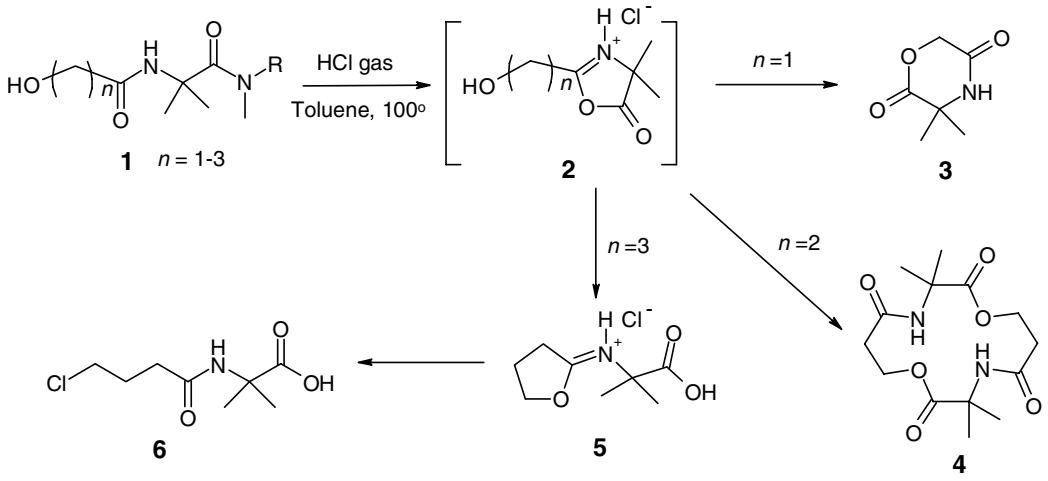
Cyclic depsipeptides are a class of biologically active secondary metabolites, which contain not only amide bonds as part of their ring structure, but also other bonds, usually lactone bonds. Their biological activity is diverse, being based mainly on their capability to transport selectively metal ions through cell membranes, and they are sought after as potential anticancer, antiviral, antibiotic and anti-inflammatory drugs [1].

One of the many methods known for their synthesis is the direct amide cyclization [2]: a suspension of an amide of type **A** in toluene is treated with dry HCl gas. Cyclization by elimination of the corresponding ammonium chloride leads to the intermediate 1,3-oxazol-5(4*H*)-one of type **B**. In the absence of other nucleophiles, **B** undergoes a ring enlargement *via* intramolecular nucleophilic attack of the hydroxy group at the carbonyl C-atom of the neighboring lactone group, to give the cyclodepsipeptide **C** (*Scheme 1)*.



Scheme 1

This method has been used successfully for the synthesis of 6-, 9-, 12- and 15-membered [3] and larger ring systems [4]. For example, α-hydroxy acid derivatives of type **1** (*n* = 1) under the 'direct amide cyclization' conditions led to morpholinediones of type **3** [5] (*Scheme 2)*. Recently, we have shown that diamides of type **A**, which contain β-hydroxy acids, *i.e.* **1** (*n* = 2), under these reaction conditions did not give the expected 7-membered cyclodepsipeptides, and only their dimers, the 14-membered rings **4** were isolated in good yields [6][7] (*Scheme 2*). Treatment of γ-hydroxy acid derivatives (**1**, *n* = 3) with HCl gas in toluene yielded no cyclodepsipeptides at all. Instead, the only products isolated were the hydrochlorides of imino lactones **5,** which are unstable in solution and isomerize in polar solvents or on silicagel to give the chlorinated acids **6** [8] (*Scheme 2*).

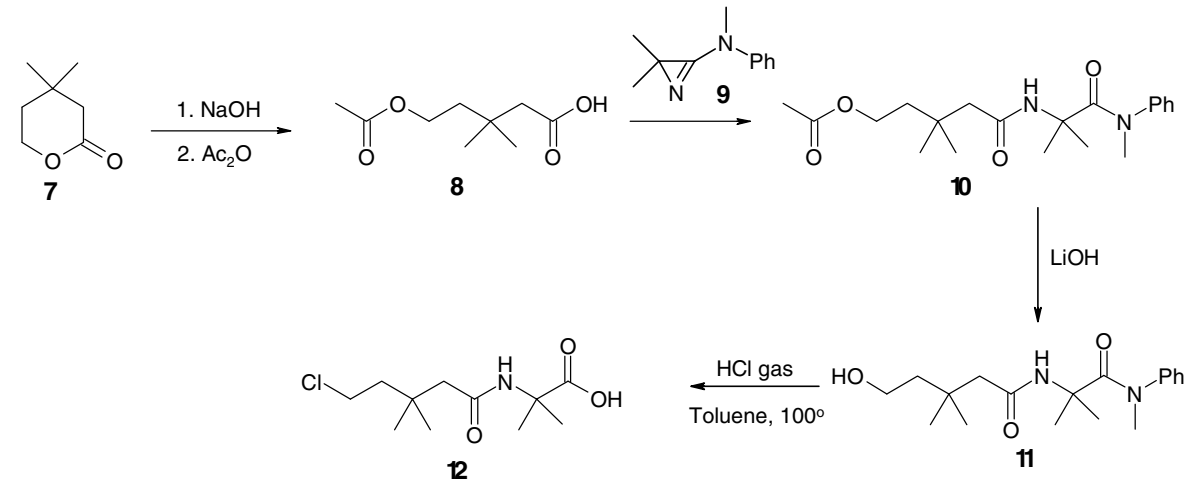


Scheme 2

In all cases so far, the formation of the intermediate oxazolone **2** was proven chemically or by IR spectroscopy. The results show that there is a relationship between the number of C-atoms between the OH and CONH groups and the type of product formed. Therefore, it was of interest to subject δ-hydroxy acid amides **1** (*n* = 4) to the conditions of the 'direct amide cyclization', which could yield either a 9- or 18-membered cyclodepsipeptide on the one hand, or a 6-membered imino lactone on the other. The result of a first example is shown below.

2. Results and Discussion

Since the previously used standard methods for syntheses of β- and γ-hydroxy acids [8] were not applicable to their δ-hydroxy analogues, we used the method of *Goto et al.* [9]: 3,3-dimethyl-γ-butyrolactone **7** was treated with NaOH and Ac_2O, which led to the O-protected 5-acetoxy-3,3-dimethylpentanoic acid (**8**) in moderate yield (*Scheme 3*).



Scheme 3

The reaction of the acid **8** with 2,2,*N*-trimethyl-*N*-phenyl-2*H*-azirin-3-amine (**9**) [10] yielded the protected diamide **10.** After deprotection with LiOH, **11** was subjected to the 'direct amide cyclization' (DAC) conditions (HCl gas, toluene, 100°). Trituration of the crude product with CH_2Cl_2, a procedure that has allowed the isolation of the imino lactone hydrochlorides **5** without isomerization to the corresponding chlorinated acids [8], yielded in the present case the chloro acid **12** directly as the only product in good yield. Recrystallization from MeCN gave crystals which were suitable for an X-ray crystal structure determination (*Fig*. 1).

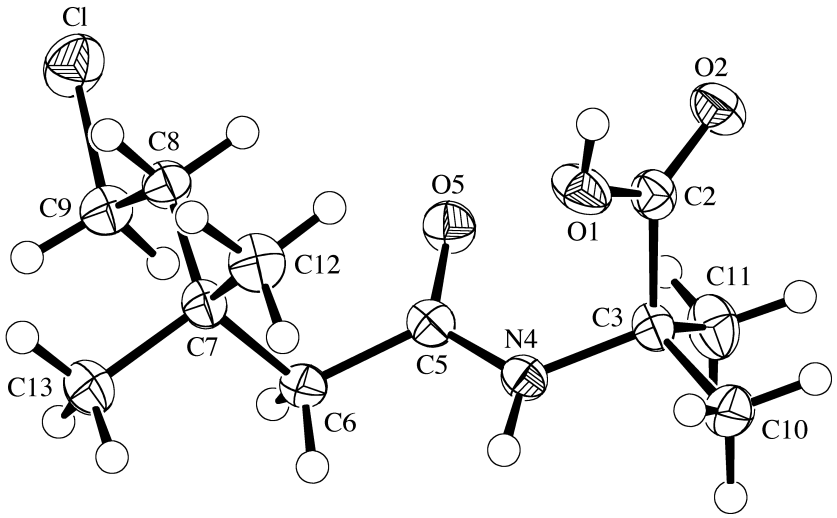


Fig. 1. ORTEP *Plot* [11] *of the molecular structure of* **12** *(arbitrary numbering of the atoms; 50% probability ellipsoids)*

Although the compound is achiral, it has crystallized in a polar space group and the absolute structure has been determined unambiguously. The OH group forms an intermolecular H-bond with the amide O-atom of a neighboring molecule, thereby linking the molecules into extended chains, which run parallel to the [0 1 0] direction and can be described by a graph set motif [12] of C(7). The amide group forms an intermolecular H-bond with the carboxylate carbonyl O-atom of a different neighboring molecule. This interaction links the molecules into extended chains, which run parallel to the [1 0 0] direction and can be descdibed by a graph set motif of C(5). The combination of both interactions generates a two-dimensional framework that lies parallel to the (0 0 1) plane (*Fig*. *2*).

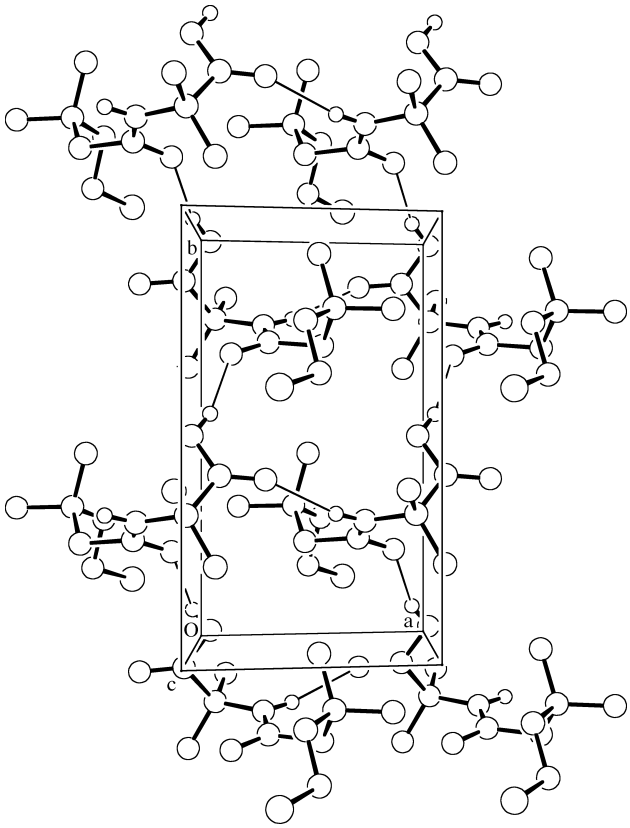
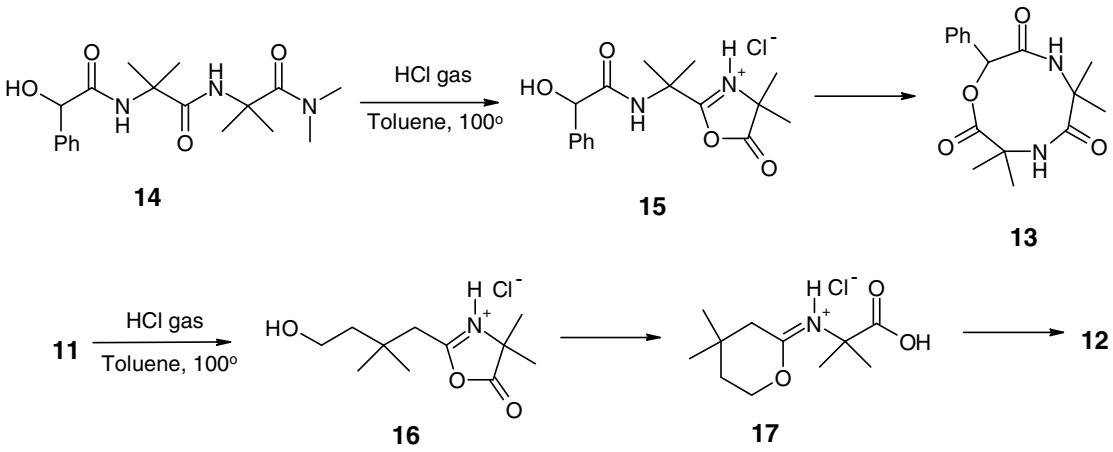


Fig. 2. *Molecular packing of* **12**, *showing the H-bonding interactions*

In our earlier studies, the ring size has a controlling influence over which of the possible products is formed from compounds of type **1** under the DAC conditions. With β-hydroxy acids (*n* = 2, *Scheme 2*) 14-membered rings **4** (cyclodimers) are preferred over 7-membered ones, while the formation of 5-membered imino lactones **5** is preferred over the corresponding 8-membered

cyclodepsipeptides in the case of γ-hydroxy acids (*n* = 3). Therefore, the expected product in the case where **1** contains a δ-hydroxy acid was either a 6-membered imino lactone analogous to **5,** or a 9-membered cyclodepsipeptide. As the 9-membered cyclodepsipeptide **13** has already been synthesized *via* DAC from the linear precursor **14** [3][13] (*Scheme 4*), the formation of **12** was a surprise.



Scheme 4

The formation of **12** proceeds most probably through the intermediate 1,3-oxazolone derivative **16** and the 6-membered imino lactone **17**, which apparently is unstable under these conditions and, by analogy with **5,** isomerizes spontaneously to give the chloro acid **12.**

3. Conclusions

The DAC conditions were applied to the linear precursor **11,** which contains a δ-hydroxy acid. Surprisingly, no cyclic depsipeptide was formed under these conditions. Thus, the dependence of the result of the DAC reaction on whether an α-, β-, γ-, or δ-hydroxy acid diamide is used has been confirmed. The general use of the 'direct amide cyclization' for the synthesis of cyclic depsipeptides is apparently limited to linear precursors which contain α-hydroxy acid amides. The use of β-hydroxy acid precursors is also possible for the formation of larger rings [4], but can lead to cyclodimers or side products as well.

Experimental Part

1. *General*. See [8].

2. *Starting materials*. 2,2,*N*-Trimethyl-*N*-phenyl-2*H*-azirin-3-amine (**9**) was prepared according to standard procedures (*cf.* [8] and refs. cited therein). Butyrolactone **7** was prepared by a known method [14].

3. *5-Acetoxy-3,3-dimethylpentanoic acid* (**8**). To a soln. of **7** (20 mmol, 2560 mg) in MeOH (10 ml) was added 2N NaOH (11 ml) at 0°. The mixture was stirred at r.t. for 2 h, the solvent evaporated *i.v.* and the remaining H_2O was distilled azeotropically with benzene (3 x 10 ml). The white residue was dried overnight under *h.v.* and then Ac_2O (10 ml) was added. After 14 h at 80°, the mixture was cooled, the solvent evaporated and the oily residue extracted with AcOEt (5 x 30 ml). Drying ($MgSO_4$) and CC on SiO_2 with CH_2Cl_2/MeOH 20:1 yielded 1201 mg (32%) of **9.** Recovered starting material: 980 mg (37%). IR: 3288*s* (br), 2971*s*, 1738v*s*, 1711v*s*, 1471*w*, 1378*s*, 1356*m*, 1244*s*, 1094*s*, 1040*s*, 925*w*. ^{1}H-NMR: 0.97 (*s*, Me_2C); 1.59-1.71 (*m*, CH_2); 1.99 (*s*, MeCO); 2.21 (*s*, CH_2); 4.01 (br. *s*, CH_2O); 10.41 (br. *s*, COOH). ^{13}C-NMR: 20.7 (*q*, *Me*CO); 27.2 (*q*, *Me*$_2$C); 32.0 (*s*, Me$_2$*C*), 37.6, 43.9 (2*t*, 2 CH_2); 66.6 (*t*, CH_2O); 171.1 (*s*, C=O); 177.3 (*s*, COOH). ESI-MS: 211 (100, $[M + Na]^+$).

4. *4-[1-Methyl-1-(*N-*methyl*-N-*phenylcarbamoyl)ethylcarbamoyl)-3,3-dimethylbutyl Acetate* (**10**). To a soln. of **8** (376 mg, 2 mmol) in dry THF (20 ml), **9** (365 mg, 2.1 mmol) was added. The mixture was stirred at r.t. overnight and the solvent evaporated *i.v.* CC with CH_2Cl_2/MeOH 40:1 yielded 622 mg (86%) of **10**. White powder. M.p. 98.1-99.4°. ^{1}H-NMR: 0.97, 1.41 (2*s*, 2 Me_2C); 1.62 (*t*, *J* = 7.1, CH_2); 1.99 (*s*, MeCO); 2.08 (*s*, CH_2); 3.19 (*s*, MeN); 3.1 (*t*, *J* = 7.1, CH_2O); 6.55 (*s*, NH); 7.20-7.39 (*m*, 5 arom. H). ^{13}C-NMR: 20.8 (*q*, *Me*CO); 26.3, 27.0 (2*q*, 2 *Me*$_2$C); 33.0 (*s*, Me$_2$*C*); 41.3 (*t*, CH_2); 42.3 (*q*, MeN); 48.2 (*t*, CH_2); 58.1 (*s*, Me$_2$*C*); 68.7 (*t*, CH_2O); 127.8, 128.0, 129.3 (3*d*, 5 arom. CH); 144.6 (*s*, arom. C); 169.8, 171.6, 173.2 (3*s*, 3 C=O). ESI-MS: 385 (100, $[M + Na]^+$]).

5. *5-Hydroxy-3,3-dimethyl*-N-*[1-methyl-1-(*N-*methyl*-N-*phenylcarbamoyl)ethyl]-pentanamide* (**11**). A soln. of **9** (362 mg, 1 mmol) in THF/H_2O 2:1 (20 ml) was treated with 4 equiv. of LiOH at r.t. for 4 h. Evaporation of the solvent *i.v.*, extraction of the residue with CH_2Cl_2, drying ($MgSO_4$), evaporation *i.v.* and washing with Et_2O yielded the hydroxydiamide **11**, which was used without further purification. Yield: 298 mg (93%) of **11**. White solid. M.p. 128.4-126.0°. ^{1}H-NMR: 0.99, 1.46 (2*s*, 2 Me_2C); 1.60 (*t*, *J* = 7.1, CH_2); 2.00 (*s*, CH_2); 3.17 (*s*, MeN); 3.18 (*t*, *J* = 7.1, CH_2O); 6.51 (*s*, NH); 7.18-7.36 (*m*, 5 arom. H). ^{13}C-NMR: 26.4, 28.8 (2*q*, 2 *Me*$_2$C); 32.8 (*s*, Me_2*C*); 41.4 (*t*, CH_2); 42.4 (*q*, MeN); 48.2 (*t*, CH_2); 58.2 (*s*, Me_2*C*); 69.7 (*t*, CH_2O); 127.8, 128.0, 129.3 (3*d*, 5 arom. CH); 144.5 (*s*, arom. C); 171.7, 173.3 (2*s*, 2 C=O). ESI-MS: 343 (100, $[M + Na]^+$).

6. *2-(5-Chloro-3,3-dimethylpentanoylamino)-2-methylpropanoic Acid* (**12**). A suspension of **11** (80 mg, 0.25 mmol) in dry toluene (30 ml) was heated to 100° and HCl gas was bubbled through the suspension for 4-6 min. Then, the mixture was allowed to cool to r.t. while bubbling N_2 through it (*ca*. 20 min). The solvent was evaporated, the white residue was washed with CH_2Cl_2 (3 x 15 ml) and dried in *h.v*. Yield: 36 mg (59%) of **12**. M.p. 118.9-121.0°. IR: 3320v*s*, 2980*s*, 1722v*s*, 1620*s*, 1561*s*, 1466*s*, 1428*s*, 1389*m*, 1246*m*, 1232*m*, 1166*s*, 1092*m*, 1051*w*, 945*w*. ^{1}H-NMR ((D$_6$)DMSO): 0.97, 1.33 (2*s*, 2 Me_2C); 1.68-1.79 (*m*, CH_2); 1.97 (*s*, CH_2); 3.60-3.69 (*m*, CH_2Cl); 7.82 (br. *s*, NH); 11.81 (br. *s*, COOH). ^{13}C-NMR ((D$_6$)DMSO): 24.8, 27.2 (*q*, *Me*$_2$C); 33.4, 42.5 (*t*, CH_2); 54.6 (*t*, CH_2Cl); 55.7 (*s*, Me_2*C*); 169.9, 175.4 (2*s*, 2 C=O). ESI-MS: 274 (25, $[M(^{37}Cl) + Na]^+$), 272 (100, $[M(^{35}Cl) + Na]^+$), 214 (10, $[M - Cl]^+$).

7. *X-Ray Crystal-Structure Determination of* **12** (*Table* and *Figs. 1*,*2*).[1]) All measurements were made on a *Nonius KappaCCD* area-detector diffractometer [15] using graphite-monochromated MoK_α radiation (λ 0.71073 Å) and an *Oxford Cryosystems Cryostream 700* cooler. The data collection and refinement parameters are given in the *Table* and views of the molecules are shown in *Figs. 1* and *2*. Data reduction was performed with *HKL Denzo* and *Scalepack* [16]. The

[1]) CCDC- 286116 contains supplementary crystallographic data for this paper. These data can be obtained free of charge form the *Cambridge Crystallographic Data Centre, via* http://www.ccdc.cam.ac.uk/data_request/cif

intensities were corrected for *Lorentz* and polarization effects, and an absorption correction based on the multi-scan method [17] was applied. Equivalent reflections, other than *Friedel* pairs, were merged. The structure was solved by direct methods using *SIR92* [18], which revealed the positions of all non-H-atoms. The non-H-atoms were refined anisotropically. The hydroxy and amide H-atoms were placed in the positions indicated by a difference electron density map and their positions were allowed to refine together with individual isotropic displacement parameters. All remaining H-atoms were placed in geometrically calculated positions and refined using a riding model where each H-atom was assigned a fixed isotropic displacement parameter with a value equal to $1.2U_{eq}$ of its parent C-atom ($1.5U_{eq}$ for the methyl groups). Refinement of the structure was carried out on F^2 using full-matrix least-squares procedures, which minimised the function $\Sigma w(F_o^2 - F_c^2)^2$. A correction for secondary extinction was applied. Refinement of the absolute structure parameter [19][20] yielded a value of 0.01(6), which confirms that the refined model represents the true absolute structure. Neutral atom scattering factors for non-H atoms were taken form [21] and the scattering factors for H-atoms were taken from [22]. Anomalous dispersion effects were included in F_c [23]; the values for f' and f'' were those of [24]. The values of the mass attenuation coefficients are those of [25]. All calculations were performed using for the *SHELXL97* program [26].

Table. *Crystallographic Data of* **12**

	12
Crystallized from	CH_3CN
Empirical formula	$C_{11}H_{20}ClNO_3$
Formula weight [g mol^{-1}]	249.74
Crystal color, habit	colorless, plate
Crystal dimensions [mm]	$0.02 \times 0.20 \times 0.25$
Temp. [K]	160(1)
Crystal system	monoclinic
Space group	$P2_1$
Z	2
Reflections for cell determination	45269
2θ range for cell determination [°]	4–55
Unit cell parameters a [Å]	6.1314(3)
b [Å]	10.4871(5)
c [Å]	10.4750(5)
β [°]	104.760(2)
V [Å^3]	651.32(5)
D_X [g cm^{-3}]	1.273
μ(MoK_α) [mm^{-1}]	0.286
Scan type	ϕ and ω
2θ(max) [°]	55
Transmission factors (min; max)	0.864; 0.996
Total reflections measured	13304
Symmetry independent reflections	2950
Reflections with $I > 2\sigma(I)$	2548
Reflections used in refinement	2950
Parameters refined; restraints	159; 1
R [on F; $I > 2\sigma(I)$ reflections]	0.0372
wR [on F^2; all indept. reflections]	0.0814
Weighting parameters [a; b][a])	0.0314; 0.1588
Goodness of fit	1.044
Secondary extinction coefficient	0.035(5)
Final Δ_{max}/σ	0.001
$\Delta\rho$ (max; min) [e Å^{-3}]	0.19; -0.16

a) $w^{-1} = \sigma^2(F_o^2) + (aP)^2 + bP]$ where $P = (F_o^2 + 2F_c^2)/3$

REFERENCES

[1] C. E. Ballard, H. Yu, B. Wang, *Curr. Med. Chem.* **2002**, *9*, 471.

[2] D. Obrecht, H. Heimgartner, *Helv. Chim. Acta* **1990,** *73*, 221.

[3] D. Obrecht, H. Heimgartner, *Helv. Chim. Acta* **1987,** *70*, 329.

[4] K. N. Koch, A. Linden, H. Heimgartner, *Tetrahedron* **2001,** *57*, 2311; K. N. Koch, H. Heimgartner, *Helv. Chim. Acta* **2000,** *83*, 1881.

[5] A. Budzowski, A. Linden, H. Heimgartner, *Heterocycles* **2004,** *64*, 417; A. Linden, F. Ghorbani-Salman Pour, R. Breitenmoser, H. Heimgartner, *Acta Crystallogr., Sect. C* **2001,** *57*, 634.

[6] B. Iliev, A. Linden, H. Heimgartner, *Helv. Chim. Acta* **2003,** *86*, 3215.

[7] B. Iliev, A. Linden, R. Kunz, H. Heimgartner, *Tetrahedron*, submitted.

[8] B. Iliev, A. Linden, H. Heimgartner, *Helv. Chim. Acta*, submitted.

[9] G. Goto, K. Okamoto, T. Okutani, I. Imada, *Chem. Pharm. Bull.* **1985**, *33*, 4422.

[10] H. Heimgartner, *Angew. Chem. Int. Ed.* **1991,** *30*, 238.

[11] C. K. Johnson, 'ORTEP II', Report ORNL-5138, Oak Ridge National Laboratory, Oak Ridge, Tennessee, 1976.

[12] J. Bernstein, R. E. Davis, L. Shimoni, N.-L. Chang, *Angew. Chem. Int. Ed.* **1995,** *34*, 1555.

[13] D. Obrecht, H. Heimgartner, *Tetrahedron Lett.* **1983,** *24*, 1921.

[14] R. Murray, D. Shiang, M. Singh, *J. Org. Chem.* **1991**, *56*, 3677.

[15] R. Hooft, *KappaCCD Collect Software*, Nonius BV, Delft, The Netherlands, 1999.

[16] Z. Otwinowski, W. Minor, in 'Methods in Enzymology', Vol. 276, 'Macromolecular Crystallography', part A, Eds. C. W. Carter Jr., R. M. Sweet, Academic Press, New York, 1997, p. 307.

[17] R. H. Blessing, *Acta Crystallogr., Sect A* **1995**, *51*, 33.

[18] A. Altomare, G. Cascarano, C. Giacovazzo, A. Guagliardi, M. C. Burla, G. Polidori, M. Camalli, SIR92, *J. Appl. Crystallogr.* **1994**, *27*, 435.

[19] H. D. Flack, G. Bernardinelli, *Acta Crystallogr., Sect A* **1999**, *55*, 908.

[20] H. D. Flack, G. Bernardinelli, *J. Appl. Crystallogr.* **2000**, *33*, 1143.

[21] E. N. Maslen, A. G. Fox, M. A. O'Keefe, in 'International Tables for Crystallography', Ed. A. J. C. Wilson, Kluwer Academic Publishers, Dordrecht, 1992 Vol. C, Table 6.1.1.1, p. 477.

[22] D. C. Creagh, W. J. McAuley, in 'International Tables for Crystallography', Ed. A. J. C. Wilson, Kluwer Academic Publishers, Dordrecht, 1992 Vol. C, Table 4.2.6.8, p. 219.

[23] D. C. Creagh, J. H. Hubbell, in 'International Tables for Crystallography', Ed. A. J. C. Wilson, Kluwer Academic Publishers, Dordrecht, 1992 Vol. C, Table 4.2.4.3, p. 200.

[24] R. F. Steward, E. R. Davidson, W. T. Simpson, *J. Chem. Phys.* **1965**, *42,* 3175.

[25] J. A. Ibers, W. C. Hamilton, *Acta Crystallogr*. **1964,** *17,* 781.

[26] G. M. Sheldrick, SHELXL97, Program for the Refinement of Crystal Structures, University of Göttingen, Germany, 1997.

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